In Hospital Measurement of Left Ventricular Ejection Fraction and One-Year Outcomes in Acute Coronary Syndromes: Results from the IMMEDIATE Trial

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ABSTRACT

Acute coronary syndromes (ACS) remain a leading cause of morbidity and mortality in the United States. Reduced left ventricular ejection fraction (LVEF) is a known marker for increased mortality, and 30-day LVEF determined by clinical study core centers following ACS is an established indicator of poor clinical outcome. However, the relationship between LVEF measured during hospitalization for ACS and the occurrence within one year of death or heart failure (HF) are less well-defined. We hypothesized that reduced in-hospital LVEF was a marker of increased risk of death or HF hospitalization at one year. As a secondary goal, we tested whether in-hospital LVEF was higher among IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care) Trial participants randomized to glucose-insulin-potassium (GIK) as compared to those randomized to placebo.

We did a retrospective analysis of participants in the IMMEDIATE Trial who had LVEF measured by cardiac catheterization or echocardiogram during hospitalization (N = 445). Adjusting for age and history of coronary artery disease (CAD), lower LVEF was significantly associated with one-year mortality or hospitalization for HF. For every 5% LVEF reduction, the hazard ratio [HR] was 1.26 (95% CI: 1.15, 1.38, $P < 0.001$); participants with LVEF < 40% had higher hazard of one-year mortality or hospitalization for HF than those with LVEF $\geq$ 40 (HR 3.59; 95% CI: 2.05, 6.27, $P < 0.001$). The HRs for the association of LVEF with the study outcomes were similar whether measured by cardiac catheterization or by echocardiography, (respectively, HR 1.32; 95% CI: 1.15, 1.51 and 1.21; 95% CI: 1.106, 1.35, interaction $P = 0.32$) and whether done within 24 hours or not within 24 hours (respectively, HR 1.28; 95% CI: 1.10, 1.50 and 1.23; 95% CI: 1.10, 1.38, interaction $P = 0.67$).

Lower in-hospital LVEF was associated with higher rates of one-year mortality and hospitalization for HF in patients hospitalized with ACS, regardless of the method of LVEF assessment, or the timing during hospitalization. This has prognostic implications for clinical practice and suggests the possibility of using various methods of LVEF determination in clinical research.

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ACI-TIPI: acute cardiac ischemia time-insensitive predictive instrument

ACS: acute coronary syndromes

AMI: acute myocardial infarction

CAD: coronary heart disease

ECG: electrocardiogram

ED: emergency department

GIK: glucose-insulin-potassium

HF: heart failure

HR: hazard ratio

IMMEDIATE: Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care

LVEF: left ventricular ejection fraction

PCI: percutaneous coronary intervention

STEMI: ST segment elevation myocardial infarction

INTRODUCTION

Acute coronary syndromes (ACS) remain a leading cause of death in the United States.(1) Reduced left ventricular ejection fraction (LVEF) measured with standardized methods at 30-days following ACS is an established marker of poor clinical outcome,(2, 3) but the relationships between LVEF measured routinely during hospitalization for ACS and clinical outcomes are less well-defined. Moreover, LVEF measured by echocardiography and ventriculography has been used to risk stratify patients with ACS,(4-7) but the best modality and timing of measurement of in-hospital LVEF are not known.

In the IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care) Trial,(8) at one-year assessment, participants with suspected ACS who received intravenous glucose-insulin-potassium (GIK) had generally fewer serious outcomes than those treated with placebo, but the differences did not reach statistical significance.(9) However, among those presenting with ST elevation myocardial infarction (STEMI), the composite outcomes of cardiac arrest or one-year mortality, and of cardiac arrest, mortality, or hospitalization for heart failure (HF) were significantly reduced.(9) Acutely, left ventricular remodeling is a dynamic time-dependent process that can result in a greater loss in systolic function with time, or, by comparison, improvements in LVEF can also be found attributed to recovery of myocardium from ischemia and stunning following revascularization. The heterogeneity of LV contractile changes during hospitalization for ACS, underscores the importance of understanding the process of remodeling across multiple time points.

While reduced LVEF at 30-days following ACS is an established marker of poor clinical outcome the relationship between LVEF measured during the hospitalization for ACS and clinical outcomes in the current era of revascularization and aggressive medical therapy is less well defined. Long-term outcomes based on LVEF routinely measured during hospitalization for ACS, in general, and in

the context of GIK, have not been studied. Using data from the IMMEDIATE Trial, we asked whether LVEF measured during hospitalization was associated with the composite outcome of all cause mortality or hospitalization for HF at one year.

We hypothesized that reduced in-hospital LVEF was a marker of increased risk of death or HF hospitalization at one year. As a secondary goal, we tested whether in-hospital LVEF was higher among IMMEDIATE Trial participants randomized to GIK as compared to those randomized to placebo.

METHODS

Study Sample

This study analyzed a subset of data on participants enrolled in the IMMEDIATE Trial. (8, 10) In brief, it was a randomized, placebo-controlled, double-blind clinical effectiveness trial of GIK conducted from December 2006 through July 2011, in which paramedics, aided by electrocardiograph-based decision support, enrolled 871 patients aged ≥ 30 years with high probabilities of ACS. Participants were given either GIK (30% glucose, 50 U/L of regular insulin, and 80 mEq of potassium chloride/L) intravenously at 1.5 mL/kg/h for 12 hours, or identical-appearing placebo. This investigation included the subset of participants who had their LVEF measured during their index hospitalization by cardiac catheterization or echocardiogram.(8,10)

Inclusion and Exclusion Criteria from the IMMEDIATE Trial

Screened patients included all those transported by emergency medical services (EMS) in response to a 9-1-1 call for symptoms suggestive of ACS who were at least 30 years of age and had an out-of-hospital electrocardiogram (ECG) performed. Inclusion was based on paramedics' clinical assessment of a patient likely having ACS, supplemented by decision support by the electrocardiograph-based Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) and Thrombolytic Predictive Instrument (TPI). Patients were candidates for enrollment if the ACI-TIPI prediction of ACS was 75% or higher, if STEMI was detected by the TPI, and/or the patient met local standards for EMS identification of STEMI.(10) Patients were excluded who had a language barrier or impaired reasoning, were prisoners or pregnant women, or had clinically significant rales (Killip Class 3 or 4 HF).(8, 10)

Data Collection

Data were collected by trained study staff. They were instructed to record LVEF as measured by cardiac catheterization; if the catheterization was not done, and LVEF was available by echocardiogram, this was recorded. The dates and times of echocardiograms were not routinely recorded, so medical records were reviewed to obtain them where possible. Based on emergency department (ED) presentation date and dates of LVEF measurement by cardiac catheterization or two-dimensional echocardiogram, we classified a participant's LVEF as "early" if they had their LVEF measured within 24 hours of ED presentation, or "not early" if measured more than 24 hours after ED presentation. We could not find dates and times for when the LVEF was measured for 94 out of 445 participants; for this study we assigned them to the not early group, as the majority (92) had echocardiograms, and our search showed that the majority of the echocardiograms were done more than 24 hours after ED presentation.

Data Analysis

Statistical analyses were performed using R, version 2.15.2. Tests were two-sided, using alpha ≤ 0.05 as statistical significance. Comparison of means of in-hospital LVEF between the GIK and placebo groups, between early vs. late LVEF measurement, and between catheterization and echocardiogram measurement all used two-sample student t-tests. Just for the Kaplan–Meier survival curves, they were plotted for participants with LVEFs in normal (55-70%), mildly abnormal (40-54%), moderately abnormal (25-39%) and severely abnormal (<25%) categories. Cox proportional hazards models were used to estimate univariate hazard ratios (HRs) for LVEF associated with the composite outcome of death or hospitalization for HF. Based on clinical and statistical significance in those analyses, we chose candidate variables for possible inclusion in a multivariable model to estimate adjusted HRs for the composite outcome of death or

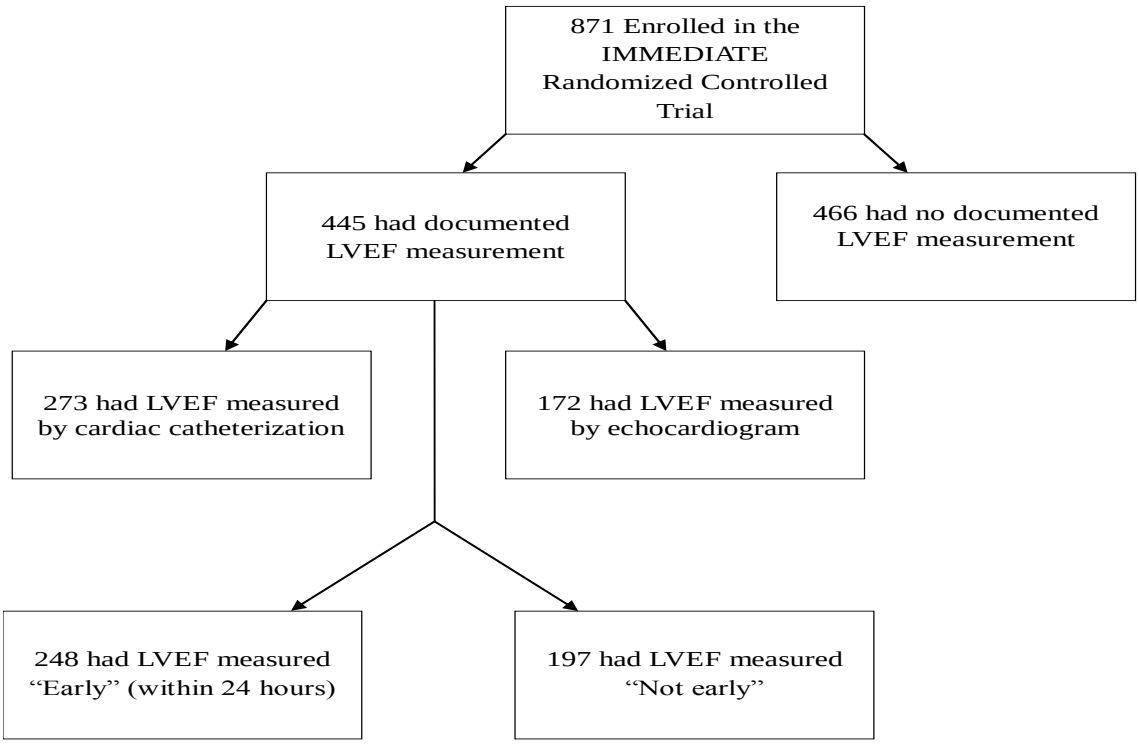
hospitalization for HF at one year. Using the final adjusted model, we also tested for dichotomous variables of timing of LVEF (early vs. not early) and the measurement method (catheterization or echocardiogram). Two-way interactions between LVEF and timing (early vs. not early) were tested in the Cox proportional hazard model of the composite outcome, adjusting for age and CAD. A similar analysis was done to test the two-way interaction between LVEF and test method (catheterization vs. echocardiogram). We checked assumptions needed for proportional hazards analyses by plotting and testing Schoenfeld residuals as related to time.

RESULTS

Baseline Demographics

Figure 1 below shows the flow diagram of the participants with LVEF and outcomes (study cohort)**.** Table 1 (see next page) shows demographic and clinical features of participants for those having the composite outcome of death or hospitalization for HF at one year (n = 52) and for those who did not (n = 393). Participants with the composite outcomes were older and more frequently had medical histories of coronary artery disease (CAD), HF, diabetes, hypertension, stroke, and hyperlipidemia. Rates of acute myocardial infarction were similar in both groups, but those participants that had the composite outcome presented with a significantly higher Killip Class.

Figure 1. Participants in the LVEF and Outcomes, Substudy of the IMMEDIATE Trial



Abbreviations: LVEF, left ventricular ejection fraction.

Table 1. Baseline Characteristics of Participants with LVEF and Outcomes (N=445)

Variables	**Participants with neither death nor hospitalization for HF at 1 year N=393**	**Participants with death or hospitalization for HF at 1 year N=52**
Age *(mean ± SD, years)*	61 ± 12.1 (393)	71 ± 13.0 (52)
Gender, % Male	75.6 (297)	69.2 (36)
White race (vs. non- White race)	86.7% (341)	88.5% (42)
Body Mass Index, (mean ± SD, units)	28.9 ± 6.3 (372)	27.9 ± 6.0 (42)
Time from onset of symptoms to treatment (minutes)		
Mean ± SD,	146.8 ± 206.4 (353)	111.7 ± 109.3 (37)
median <IQR>	78 < 50.0-140.0 >	65 < 40.0-145.0 >
Chief Complaint on Presentation		
Chest Pain	91.8% (361)	84.6% (44)
Medical History, % (n)		
CAD (MI, PCI or CABG)	30.8% (121)	69.2% (36)
Heart Failure	6.7% (25)	23.1% (12)
Diabetes Mellitus	21.1% (83)	34.7% (18)
Hypertension	62.3% (245)	78.8% (41)
Stroke	5.9% (23)	15.4% (8)
Hyperlipidemia	46.8% (184)	65.4% (34)
Hospital Reperfusion Treatment, %(n)		
PCI	73.8% (290)	59.6% (31)
Thrombolytic therapy	0.8% (3)	9.6% (5)
CABG	5.1% (20)	7.7% (4)
Confirmed Diagnosis, % (n)		
Acute Myocardial Infarction	80.4% (316)	78.8% (41)
Killip Class		
1	76.1% (299)	51.9% (27)
2	1.8% (7)	1.3% (7)
3	0.5% (2)	3.8% (2)
4	2.0% (8)	9.6% (5)
Unstable Angina	12.7% (50)	9.6% (5)
ECG based findings		
ST Elevation on Presentation (ECG)	70.8% (264)	66.0% (33)
ACI-TIPI score, (Mean ± SD)	80.7 ± 17.6 (386)	84.8 ± 11.2 (49)
LVEF in %, Median (IQR)	50 (40,60)	35 (25,45)
GIK (vs. Placebo)	47.6% (187)	38.5% (20)

Abbreviations: ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; CABG, coronary artery bypass graft; ECG, electrocardiogram; GIK, glucose-insulin-potassium; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

Data on LVEF measured by cardiac catheterization or two-dimensional echocardiogram during the index hospitalization were available for 445 out of the 871 study participants. There were significant differences in baseline demographics and clinical characteristics of participants with and without in-hospital LVEFs recorded as seen in Table 2 below.

Table 2. Baseline Characteristics of Participants with In-hospital LVEF Compared with Participants without LVEF (N = 891)

Variables	**Participants with in-hospital LVEF N = 445**	**Participants without in-hospital LVEF N = 466**
Age *(mean ± SD, years)*	61.9 ± 12.6 (445)	65.4 ± 15.2 (466)
Gender, % Male	74.8% (333)	61.2% (285)
White Race (vs. Non White Race)	86.9% (387)	79.1% (337)
Body Mass Index *(Mean ± SD, units)*	28.9 ± 6.3 (414)	28.9 ± 7.0 (466)
Time from onset of symptoms to treatment (minutes)		
Mean ± SD	143.5 ± 119.4 (390)	188.6 ± 249.4 (334)
median <IQR>	77 < 48.0 - 140.8 >	92.0 < 51.25 - 2350.0 >
Chief complaint of Chest Pain	91.0% (405)	80.8% (344)
Medical History, % (n)		
CAD (MI, CABG or PCI)	35.3% (157)	51.2% (218)
Heart Failure	8.3% (37)	25.4% (108)
Diabetes Mellitus	22.7% (101)	33.1% (141)
Hypertension	64.3% (286)	72.8% (310)
Stroke	6.9% (31)	12.9% (55)
Hyperlipidemia	48.9% (218)	54.5% (232)
Confirmed Diagnosis		
Acute Myocardial Infarction	80.2% (357)	20.0% (85)
Killip Class		
1	73.3% (326)	16.9% (72)
2	3.2% (14)	1.8% (5)
3	0.9% (4)	1.8% (5)
4	2.9% (13)	0.7% (3)
Unstable Angina	12.4% (55)	13.1% (56)
ECG based findings		
ST segment elevation on presentation (ECG)	70.2% (297)	24.9% (60)
ACI-TIPI score, *(Mean ± SD)*	81.1± 8.1(435)	70.2 ± 13.7(418)

Abbreviations: ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; CABG, coronary artery bypass graft; ECG, electrocardiogram GIK, glucose-insulin-potassium; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

Of participants with in-hospital LVEF measured, 92.6% had confirmed diagnoses of ACS, compared with 33.1% among those without measured LVEF. There were no significant differences between characteristics of participants who had in-hospital LVEF recorded by catheterization vs. echocardiogram (Table 3).

Table 3. Baseline Characteristics of Participants with In-hospital LVEF Measured by Either Cardiac Catheterization or Echocardiogram (N = 445)

Variables	**Participants with LVEF measured by cardiac catheterization N = 273 (61%)**	**Participants with LVEF measured by 2-dimensional echocardiogram N = 172 (39%)**
Age *(mean ± SD, years)*	61.4 ± 12.7 (273)	62.7 ± 12.5 (172)
Gender, % Male	73.3 (200)	77.3 (133)
White race (vs. non – white race)	86.4% (236)	87.7% (151)
Body Mass Index *(Mean ± SD, units)*	28.5 ± 6.1 (254)	29.4 ± 6.6 (160)
Time from onset of symptoms to treatment (minutes)		
Mean ± SD,(n)	129.9 ± 165.9 (243)	165.9 ± 243.9 (147)
median <IQR>	75 < 50, 138 >	80 < 46.5, 157 >
Chief complaint of Chest Pain	93.0% (254)	87.8% (151)
Prior Medical History, % (n)		
History of CAD (MI, CABG or PCI)	32.9% (90)	38.9% (67)
Heart Failure	7.3% (20)	9.9% (17)
Diabetes Mellitus	21.9% (60)	23.8% (41)
Hypertension	62.3% (170)	67.4% (116)
Stroke	7.3% (20)	6.4% (11)
Hyperlipidemia	49.1% (134)	48.8% (84)
Confirmed Diagnosis		
Acute Myocardial Infarction	78.4% (214)	83.1% (143)
Killip Class		
1	74.7% (204)	70.9% (122)
2	2.2% (6)	4.7% (8)
3	0.0% (0)	2.3% (4)
4	1.5% (4)	5.2% (9)
Unstable Angina	12.1% (33)	12.8% (22)
ECG based findings		
ST segment elevation, presenting ECG	69.4% (177)	71.4% (120)
ACI-TIPI score, (*Mean ± SD*)	80.5 ± 17.6 (269)	82.1 ± 16.2 (170)
LVEF in % Median (IQR)	50 (40,60)	45 (35,55)

Abbreviations: ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; CABG, coronary artery bypass graft; ECG, electrocardiogram; GIK, glucose-insulin-potassium; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

Comparing the baseline and clinical characteristics of participants with in-hospital LVEF early versus not early showed that significantly higher percent of ST elevation on presentation (Table 4).

Table 4: Baseline Characteristics of Participants who had In-hospital LVEF Measured Early, or Not Early, Either by Cardiac Catheterization or Echocardiogram

Variables	**Participants with LVEF measured early (within 24 hours of admission) (N = 248)**	**Participants with LVEF measured not early (more than 24 hours after admission) (N = 197)**
Age *(mean ± SD, years)*	60.8 ± 12.4 (248)	63.3 ± 12.7 (172)
Gender, % male	74.2% (184)	75.6% (149)
White race (vs. Non-white race)	86.7% (215)	87.3% (172)
Body Mass Index *(Mean ± SD, units)*	28.5 ± 6.2 (230)	29.3 ± 6.4 (184)
Time from onset of symptoms to treatment (minutes)		
Mean ± SD(n)	143.9 ± 188 (223)	143.0 ± 214 (167)
median <IQR>	83 < 50.0, 145.0 >	71 < 45.0, 127.0 >
Chief complaint of Chest Pain	93.1% (231)	93.1% (231)
Prior Medical History, % (n)		
History of CAD (MI, CABG or PCI)	30.6% (76)	41.1% (81)
Heart Failure	6.5% (16)	10.6% (21)
Diabetes Mellitus	20.6% (51)	25.4% (50)
Hypertension	60.5% (150)	69.0% (136)
Stroke	5.6% (14)	8.6% (17)
Hyperlipidemia	46.8% (116)	51.7% (102)
Confirmed Diagnosis		
Acute Myocardial Infarction	81.5% (202)	78.7% (155)
Killip Class		
1	77.4% (192)	68.0% (134)
2	1.6% (4)	5.1% (10)
3	0.0% (0)	2.0% (4)
4	2.4% (6)	3.5% (7)
Unstable Angina	10.9% (27)	14.2% (28)
ECG based findings		
ST segment elevation on presentation (ECG)	77.9% (183)	60.6% (114)
ACI-TIPI score, *(Mean ± SD)*	82.1± 15.7 (241)	79.9± 18.5 (194)
LVEF in % Median (IQR)	50 (40,60)	45 (35,55)

Abbreviations: ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; CABG, coronary artery bypass graft; ECG, electrocardiogram; GIK, glucose-insulin-potassium; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

For 248 participants, LVEF was measured early (219 [80.1%] by catheterization), defined as measurement within 24 hours of presentation, and for 197 participants, the LVEF measurement was performed not early (54 [19.7%] by catheterization), or after 24 hours of presentation as seen in Table 5 below.

Table 5: Difference in Days by Catheterization and Echocardiogram (N = 445)

Timing of LVEF	Difference in days	Catheterization*	Echocardiogram†
Early	0	219	29
Not early	1	32	36
	> 1	20	15
	NA	2	92
Total		273	172

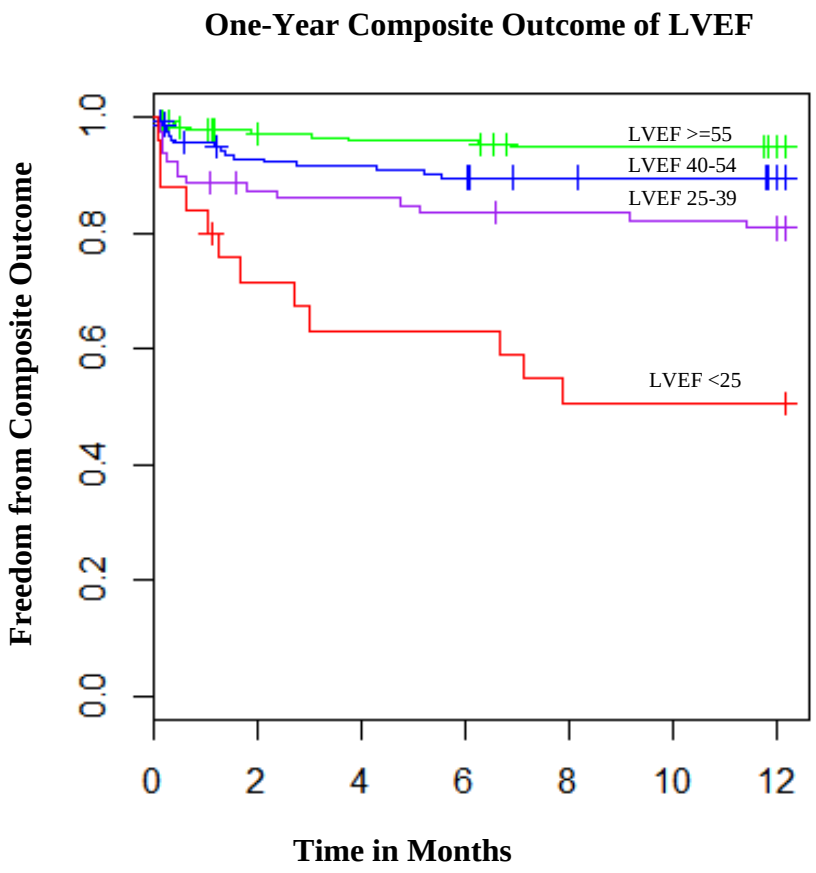
Abbreviations: LVEF, left ventricular ejection fraction
*Catheterization: Difference in days between the date of cardiac catheterization and emergency department arrival.
†Echocardiogram: Difference in days between the date of echocardiography and emergency department arrival.

Univariate Models of LVEF and Outcomes

Participants with the lowest LVEF had the lowest survival or the greatest incidence of composite outcomes (Figure 2). Univariate Cox proportional hazard models were used to identify factors associated with the composite outcome (Table 6).

A reduction of LVEF by 5% decrements was significantly associated with higher hazards of death or hospitalization for HF over one year (HR = 1.31, 95% CI: 1.20 – 1.45, P < 0.001). Also significant was age, expressed in 10-year increments (HR = 1.79, 95% CI: 1.44 – 2.24, P < 0.001), history of CAD (HR = 4.46, 95% CI: 2.47 – 8.04, P < 0.001), history of HF (HR = 3.56, 95% CI: 1.86 – 6.79, P < 0.001), history of diabetes (HR = 1.88, 95% CI: 1.06 – 3.34, P = 0.030), history of hypertension (HR = 2.17, 95% CI: 1.12 – 4.23, P = 0.022), and history of stroke (HR = 2.56, 95% CI: 1.20 – 5.43, P = 0.015).

Figure 2. Kaplan–Meier Survival Plot for Categories of LVEF



Abbreviations: LVEF, left ventricular ejection fraction.

Table 6. Unadjusted Cox Proportional Hazard Model with Composite Outcomes (Death and Hospitalization for HF)

Variables	HR (95% CI)	P-value
LVEF /5% decrease	1.31 (1.20,1.45)	< 0.001
Age/10 years increase	1.79 (1.44, 2.24)	< 0.001
Gender, Male	1.37 (0.41, 1.32)	0.23
White race (nonwhite race reference)	1.13 (0.48, 2.65)	0.77
Body Mass Index	0.97 (0.92, 1.02)	0.32
Time from onset of symptoms to treatment*	0.98 (0.99, 1.00)	0.33
Chief complaint on presentation		
Chest pain	0.53 (0.23, 1.12)	0.10
Out of Hospital ECG ST-Elevation	0.84 (0.47, 1.50)	0.55
ACI-TIPI Score	1.02 (0.99, 1.04)	0.12
Medical History		
CAD (MI, PCI or CABG)	4.46 (2.47, 8.04)	< 0.001
Heart Failure	3.56 (1.86, 6.79)	< 0.001
Diabetes	1.88 (1.06, 3.34)	0.03
Hypertension	2.17 (1.12, 4.23)	0.02
Stroke	2.56 (1.20, 5.43)	0.02

Abbreviations: ACI-TIPI, acute cardiac ischemia time-insensitive predictive instrument; CAD, Coronary artery disease; CABG, coronary artery bypass graft; CI, confidence interval; ECG, electrocardiography; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
* Per 10 minutes

Multivariable Models of LVEF and Outcomes

Multivariate Cox models were used to better characterize the association of LVEF with the composite outcome combined and separately, see Table 7 on the following page. In stepwise regression, candidate parameters for inclusion included LVEF expressed by 5% decrements; age, sex, history of CAD, HF and diabetes. The model that had the lowest akaike information criteria (AIC) (best fit) following the selection process included only LVEF, age, and CAD. The C-statistic (which is equivalent to the receiver-operating characteristic (ROC) curve area) for that model is 0.805 (SE = 0.04).

Table 7. Composite Outcomes (Combined and Separately) with LVEF Measured In-Hospital (N = 445, no of events = 52)

Variable	HR (95% CI)	P value
Outcome (Composite)		
LVEF/5% lower (combined)	1.26 (1.15, 1.38)	< 0.001
Age/10 years Increase	1.73 (1.38, 2.18)	< 0.001
History of CAD (MI, PCI, or CABG)	2.97 (1.62, 5.43)	< 0.001
Outcome (Death)		
LVEF/5% lower (combined)	1.18 (1.06, 1.32)	0.002
Age/10 years Increase	1.94 (1.47, 2.55)	< 0.001
History of CAD (MI, PCI, or CABG)	3.56 (1.69, 7.49)	< 0.001
Outcome (Hospitalization for HF)		
LVEF/5% lower (combined)	1.37 (1.18, 1.58)	< 0.001
Age/10 years Increase	1.35 (0.95, 1.91)	0.09
History of CAD (MI, PCI, or CABG)	2.27 (0.93, 5.56)	0.007

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

The effect of 5% lower LVEF on one-year death or hospitalization for HF remained statistically significant after adjusting for age and history of CAD (HR = 1.26; 95% CI: 1.15 – 1.38, $p < 0.001$), with LVEF being used as a continuous variable, when dichotomizing, participants with LVEF < 40% had higher hazard of one-year mortality and hospitalization for HF compared to participants with LVEF $\geq$ 40%, after adjusting for age and history of CAD (HR = 3.59; 95% CI: 2.05 – 6.27, $p < 0.001$), when LVEF was tested as a binary variable (Appendix C Table 1). The proportional hazard assumption was not violated. Separating the composite outcome into its components, reductions of LVEF by 5% decrements were also significantly associated with higher hazard of death and hospitalization for HF when adjusted for age and history of CAD (HR = 1.18; 95% CI: 1.06 – 1.32, P = 0.002; and HR = 1.37; 95% CI: 1.18 – 1.58, P < 0.001, respectively) (see Table 7 above).

The HRs for the association of LVEF with the study outcomes were similar whether measured by cardiac catheterization or echocardiography (respectively, HR = 1.32; 95% CI: 1.15, 1.51 and 1.21; 95% CI 1.106, 1.35), and whether done within 24 hours or not within 24 hours (respectively, HR = 1.28; 95% CI: 1.10, 1.50 and 1.23; 95% CI 1.10, 1.38). Tests for interactions of LVEF and measurement method and LVEF and timing did not reach significance as seen in Table 8 below.

Table 8. Association of LVEF with Composite Outcome, Stratified by Timing and Type of Procedure

Variable	**Adjusted HR (95% CI)**	**Interaction P value**
LVEF- by catheterization /5% lower*	1.32 (1.15, 1.51)	0.32
LVEF- by echocardiogram /5% lower*	1.20 (1.06, 1.35)	
LVEF- early /5% lower*	1.28 (1.10, 1.50)	0.67
LVEF- not early /5% lower*	1.23 (1.10, 1.38)	

Abbreviations: CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction;
*Adjusted for age and history of CAD

Controlling for method of LVEF measurement (catheterization or echocardiography) or timing of measurement (early vs. not early) did not alter the association of LVEF with the outcome (Table 9).

Table 9. Model for LVEF Measured by Cardiac Catheterization (reference Echocardiogram) and Not Early (reference Early) (N = 445, no of events = 52)

Variable	**HR (95% CI)**	**P value**
LVEF/5% lower (combined)	1.25 (1.14, 1.37)	< 0.001
Age/10 years Increase	1.71 (1.36, 2.15)	< 0.001
History of CAD (MI, PCI, or CABG)	2.94 (1.60, 5.40)	< 0.001
LVEF - echocardiogram (reference catheterization)	1.62 (0.93, 2.80)	0.08
LVEF/5% lower (combined)	1.25 (1.13, 1.36)	< 0.001
Age/10 years Increase	1.71 (1.36, 2.15)	< 0.001
History of CAD (MI, PCI, or CABG)	2.86 (1.56, 5.26)	< 0.001
LVEF - not early (reference early)	1.53 (0.86, 2.69)	0.14

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Additionally, while having an echocardiogram (vs. catheterization) and being not early (vs. early) were associated with the one-year outcome, neither was statistically significant.

Sensitivity analyses were performed in which we re-estimated HRs for LVEF, adjusting not only for already specified covariates age and CAD history, but also for sex, HF history, and diabetes. Reductions of LVEF by 5% were significantly associated with higher hazard of the one-year composite outcome (HR = 1.25; 95% CI: 1.14 – 1.38, P < 0.001). Also, the HRs for the association of LVEF with the study outcome when measured by cardiac catheterization vs. by echocardiography and for when measured early vs. not early were similar (Tables 10 and 11).

Table 10. Composite Outcome and LVEF measured by Catheterization and Echocardiogram

Variable	**Adjusted HR (95% CI)**	**P-value**
Model in subset of participants with LVEF measured by Catheterization (N = 273, No of events = 24)		
LVEF (by Catheterization)/5% lower	1.29 (1.11, 1.53)	0.002
Age/10 years increase	2.41 (1.56, 3.71)	< 0.001
Sex (Male vs Female)	1.78 (0.68, 4.65)	0.72
Medical History		
CAD (MI, PCI or CABG)	1.92 (0.80, 4.60)	0.14
Heart Failure	1.76 (0.59, 5.20)	0.30
Diabetes	0.89 (0.33, 2.37)	0.81
Model in subset of participants with LVEF measured by Echo (N = 172, No of events = 28)		
LVEF(by echocardiogram)/5% lower	1.20 (1.06, 1.36)	0.005
Age/10 years increase	1.49 (1.10, 2.03)	0.001
Sex (Male vs Female)	0.75 (0.33, 1.73)	0.50
Medical History		
CAD (MI, PCI or CABG)	3.74 (1.49, 9.37)	0.005
Heart Failure	0.63 (0.22, 1.76)	0.38
Diabetes	1.63 (0.74, 3.62)	0.22

Abbreviations: CAD, Coronary artery disease; CABG, coronary artery bypass graft; CI, confidence interval; ECG, electrocardiography; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 11. Composite Outcome and LVEF Measured Early and Not Early

Variable	Adjusted HR (95% CI)	P-value
Model in subset of participants with LVEF measured early (N = 248, no of events = 20)		
LVEF /5% lower	1.31 (1.09, 1.56)	0.002
Age/10 years increase	2.13 (1.38, 3.30)	< 0.001
Sex (Male vs Female)	2.42 (0.79, 7.36)	0.11
Medical History		
CAD (MI, PCI or CABG)	1.80 (0.75, 4.67)	0.17
Heart Failure	0.77 (0.18, 3.23)	0.72
Diabetes	1.37 (0.47, 3.98)	0.56
Model in subset of participants with LVEF measured not early (N = 197, no of events = 32)		
LVEF /5% lower	1.21 (1.07, 1.36)	0.001
Age/10 years increase	1.60 (1.20, 2.20)	0.002
Sex (Male vs Female)	0.65 (0.29, 1.43)	0.72
Medical History		
CAD (MI, PCI or CABG)	3.93 (1.60, 9.70)	0.003
Heart Failure	0.88 (0.36, 2.20)	0.80
Diabetes	1.24 (0.59, 2.60)	0.57

Abbreviations: CAD, Coronary artery disease; CABG, coronary artery bypass graft; CI, confidence interval; ECG, electrocardiography; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Finally, we studied the association of the IMMEDIATE Trial treatment, GIK vs. placebo, on in-hospital LVEF, stratified by method (catheterization vs. echocardiogram) and timing (early vs. not early) (see Table 12 on the following page). There was a trend towards higher in-hospital LVEF among those receiving GIK, especially when measured by echocardiogram, but that difference did not reach statistical significance.

Table 12. Distribution of LVEF % by Experimental Treatment Groups

Variable	**GIK,** Mean (SD) Median LVEF%, (N)	**Placebo** Mean (SD) Median LVEF%, (N)	**P value for Mean**
LVEF (Catheterization and Echocardiogram)	48.6 (14) 50 (207)	46.2 (14) 45 (238)	0.07
LVEF (Catheterization)	49.3 (14) 50 (120)	48.3 (14) 50 (153)	0.33
LVEF (Echocardiogram)	47.6 (14) 50 (87)	43.6 (14) 45 (85)	0.08
LVEF (Early*)	49.2 (13) 50 (110)	47.4 (13) 50 (138)	0.27
LVEF (Not early†)	47.8 (15) 50 (97)	44.6 (15) 45 (100)	0.13

Abbreviations: GIK, glucose-insulin-potassium; LVEF, left ventricular ejection fraction; SD, standard deviation.
* Early when the LVEF was measured within 0 days of ER arrival.
† Not early when LVEF was measured 1 or more days after ER arrival or with unknown dates.

DISCUSSION

We demonstrated the utility of measuring LVEF in-hospital for patients with ACS as a means to identify patients at risk of death or HF hospitalization within one year. Our results do not favor catheterization or echocardiography as a modality of choice for LVEF measurement; the predictive ability of LVEF for one year outcomes was the same if the assessment was performed by either modality. These results do not support a need for LVEF assessment necessarily within 24 hours of presentation. These results have practical importance for the care of patients with ACS because our data suggest that assessment of LVEF measured at any point in the hospitalization can be used to predict patients at risk of death or hospitalization for HF within one year.

In-hospital LVEF assessment is not performed in a significant number of patients with ACS. One study demonstrated as many as 40.8% of patients with non-ST elevation myocardial infarction did not have an LVEF assessment,(11,12) and the percentage of patients getting LVEF measurement has steadily increased in the last two decades.(13, 14) LVEF was superior to end systolic volume index and infarct size in predicting six–month mortality after myocardial infarction.(2) The presence of LV dysfunction identified on baseline left ventriculography in patients enrolled in the HORIZONS–AMI trial who underwent primary percutaneous coronary intervention (PCI) in the modern era was a powerful predictor of early and late mortality irrespective of the extent of coronary artery disease.(7) In spite of optimal medical therapy and clinically driven PCI, LVEF and angiographic burden of disease at baseline retain prognostic importance for patients aggressively treated for stable CAD.(16)

Our study, which featured the full spectrum of ACS presentations, suggests that useful information can be obtained by measuring LVEF by either catheterization or echocardiography

at any time prior to hospital discharge. These findings have important implications for clinical effectiveness research, because we demonstrate the utility of collecting data from clinically-indicated and performed LVEF assessments in large multicenter clinical trials as a means to define risk of longitudinal cardiac outcomes. If substantiated as a research tool, this finding has potential to reduce the need for core lab LVEF assessments, which can be quite costly.

In the IMMEDIATE Trial, GIK did not significantly reduce the primary endpoint of progression of unstable angina to AMI, but it did significantly reduce the composite endpoint of cardiac arrest or mortality, and in the biological mechanism cohort, the median infarct size measured by sestamibi SPECT imaging at 30 days was 80% lower in the GIK compared to the placebo group.(8) Further, there was a trend for better LVEF measured by SPECT imaging at 30 days with GIK.(8) Our study also showed that GIK had a trend toward improved in-hospital LVEF when compared to placebo especially when measured by echocardiogram. Future well-powered studies will be required to further delineate the effect of GIK on infarct size and long-term left ventricular function.

Our study has several limitations. It is a retrospective analysis using data from a prospective randomized controlled trial on a subset with 445 participants who had LVEF measured by echocardiogram or cardiac catheterization. While the sample is not large, we had 52 composite outcomes in the group. The study cohort includes patients with high-risk ACS. The LVEF was measured by two different modalities at slightly different times, which could introduce bias since the LVEF measured by catheterization was during revascularization and LVEF measured by echocardiogram was primarily obtained prior to hospital discharge. However, our study showed that the methodology and the timing of the LVEF measurement did not matter. The study cannot compare the in-hospital LVEF measurement with an assessment made by a core lab, and hence we cannot say that clinical LVEF results necessarily give the same

information as measurements made by a core laboratory. However, we did find that LVEF measured in the hospital and not by a core laboratory was significantly associated with one-year outcomes of death and HF hospitalization.

CONCLUSION

Lower LVEF was associated with higher rates of one-year mortality and hospitalization from HF in patients hospitalized with ACS, regardless of the method of LVEF assessment or timing, during hospitalization. This has prognostic implications for clinical practice and suggests the possibility of using various methods of LVEF determination in clinical research.

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