ORIGINAL RESEARCH

Index of Microcirculatory Resistance at the Time of Primary Percutaneous Coronary Intervention Predicts Early Cardiac Complications: Insights From the OxAMI (Oxford Study in Acute Myocardial Infarction) Cohort

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***Background*—**Early risk stratification after primary percutaneous coronary intervention (PPCI) for ST-segment–elevation myocardial infarction is currently challenging. Identification of a low-risk group may improve triage of patients to alternative clinical pathways and support early hospital discharge. Our aim was to assess whether the index of microcirculatory resistance (IMR) at the time of PPCI can identify patients at low risk of early major cardiac complications and to compare its performance against guideline-recommended risk scores.

***Methods and Results*—**IMR was measured using a pressure–temperature sensor wire. Cardiac complications were defined as the composite of cardiac death, cardiogenic shock, pulmonary edema, malignant arrhythmias, cardiac rupture, and presence of left ventricular thrombus either before hospital discharge or within 30-day follow-up. In total, 261 patients undergoing PPCI who were eligible for coronary physiology assessment were prospectively enrolled. Twenty-two major cardiac complications were reported. Receiver operating characteristic curve analysis confirmed the utility of IMR in predicting complications and showed significantly better performance than coronary flow reserve, the Primary Angioplasty in Myocardial Infarction II (PAMI-II), and Zwolle score ($P \leq 0.006$). Low microvascular resistance (IMR ≤ 40) was measured in 159 patients (61%) of the study population and identified all patients who were free of major cardiac complications (sensitivity: 100%; 95% CI, 80.5–100%).

***Conclusions*—**IMR immediately at the end of PPCI for ST-segment–elevation myocardial infarction reliably predicts early major cardiac complications and performed significantly better than recommended risk scores. These novel data have implications for early risk stratification after PPCI. **(*J Am Heart Assoc*. 2017;6:e005409. DOI: 10.1161/JAHA.116.005409.)**

Key Words: clinical outcome • microcirculation • myocardial infarction

The incidence of major in-hospital complications following ST-segment–elevation myocardial infarction (STEMI) after primary percutaneous coronary intervention (PPCI) has decreased dramatically but remains at ≈10%.[1,2] Following PPCI, patients are routinely admitted to coronary intensive care units (ICUs) for close monitoring and usually remain in the hospital for up to 72 hours, independent of their progress and clinical status, because few validated early risk-stratification tools exist to risk-stratify these patients.

Improved methods of identifying risk may have important implications for clinical management, for example, in terms of intensity of monitoring and duration of admission.[3,4] The American College of Cardiology/American Heart Association and European Society of Cardiology guidelines suggest that

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Accompanying Table S1 and Figure S1 are available at http://jaha.ahajournals.org/content/6/11/e005409/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Measurement of the index of microcirculatory resistance at the end of primary percutaneous coronary intervention for ST-segment–elevation myocardial infarction predicts major in-hospital cardiac complications and outperforms current risk stratification scores.

What Are the Clinical Implications?

- The index of microcirculatory resistance provides an objective method of risk-stratifying patients immediately after angioplasty who may be allocated to a low-risk group associated with potentially reduced need for intensive care unit admission, shorter hospital stay, and reduced hospital costs.

PPCI patients with a "low risk of complications" might be candidates for non-ICU admission[5] and early discharge.[2] They recommend the Primary Angioplasty in Myocardial Infarction II (PAMI-II) and Zwolle PPCI score as tools to potentially identify low-risk patients.[2]

Guidewire-based measurement of coronary flow and pressure is safe[6] and easily conducted at the time of PPCI. The thermodilution-derived index of microcirculatory resistance (IMR) is a specific, quantitative, and reproducible measure of microvascular function,[7,8] which predicts infarct size and left ventricular ejection fraction after an acute myocardial infarction.[9–11] Moreover, an IMR value >40, measured at the time of PPCI, is associated with adverse long-term outcomes in terms of death and rehospitalization for heart failure.[12] It is unknown whether IMR allows identification of in-hospital cardiac complications such as cardiac death, cardiogenic shock, pulmonary edema, malignant arrhythmias, or cardiac rupture and thus can be used as a tool to identify those at high risk early after PPCI.

The aims of this study were to assess the relationship between IMR measured immediately after PPCI and incidence of early cardiac complications and to compare the diagnostic performance of IMR against the guideline-recommended PAMI-II and Zwolle scores.

Methods

Patient Population and Acute Management

Patients presenting with an acute STEMI and referred for PPCI to the Oxford Heart Centre were prospectively assessed for enrollment in the study (Figure 1). STEMI was defined as ongoing chest pain and ST-segment elevation on the ECG. Exclusion criteria were safety or clinical concerns based on the operator's judgment, including PCI-related complications. PPCI was performed in the standard manner, according to international guidelines. All patients were on dual antiplatelet treatment at the time of the procedure, loaded with aspirin 300 mg and either clopidogrel 600 mg or ticagrelor 180 mg. Anticoagulation was achieved with unfractionated heparin (70- to 100-U/kg bolus followed by subsequent doses to maintain a target activated clotting time of 250–300 seconds during the procedure) in combination with abciximab (0.25-mg/kg bolus ±0.125-μg/kg per minute intravenous infusion for 12 hours) or bivalirudin (0.75-mg/kg bolus followed by an infusion of 1.75 mg/kg per minute for up to 3 hours) with bail-out abciximab. Thrombus aspiration was undertaken at the operator's discretion. The coronary physiology measurements were performed at the end of the procedure, as described in the next section.

Thereafter, all patients were admitted to a high-intensity-monitoring bed with a nurse:patient ratio of 1:1 or 1:2, staff certified in critical care, and the ability to provide advanced hemodynamic monitoring and life-sustaining mechanical cardiorespiratory support. Dual antiplatelet therapy for 12 months, angiotensin-converting enzyme inhibitor or angiotensin receptor II antagonist, beta-blocker, and statin were recommended, according to the current guidelines.

The study population was recruited as part of the Ox-AMI (Oxford Study in Acute Myocardial Infarction) cohort (REC no. 10/H0408/24).[13–16] Witnessed verbal assent was obtained from eligible patients after coronary reperfusion in the cardiac catheterization laboratory, and written informed consent was obtained on the ICU, in accordance with the principles of the Declaration of Helsinki.

Coronary Physiology Measurements

The coronary physiology indices were measured immediately at the end of the emergency coronary intervention, as described previously.[13] In brief, a combined pressure- and temperature-sensitive guidewire was calibrated outside the body, equalized with aortic pressure at the ostium of the guide catheter, and then advanced to the distal infarct-related artery. After intracoronary injection of 250 μg isosorbide dinitrate, the mean distal coronary pressure measured with the pressure wire and mean proximal coronary pressure measured with the guide catheter were recorded. Mean transit time was obtained by 3 brisk intracoronary injections of 3 mL saline at room temperature. Adenosine 140 μg/kg per minute administered via a large peripheral vein was used to induce hyperemia. During steady-state hyperemia, mean proximal coronary pressure, mean distal coronary pressure, and mean transit time were measured again. IMR was defined as the mean distal coronary pressure multiplied by the mean hyperemic transit time (mm Hg×seconds or units), coronary flow reserve (CFR) was calculated by dividing the mean resting transit time by the mean

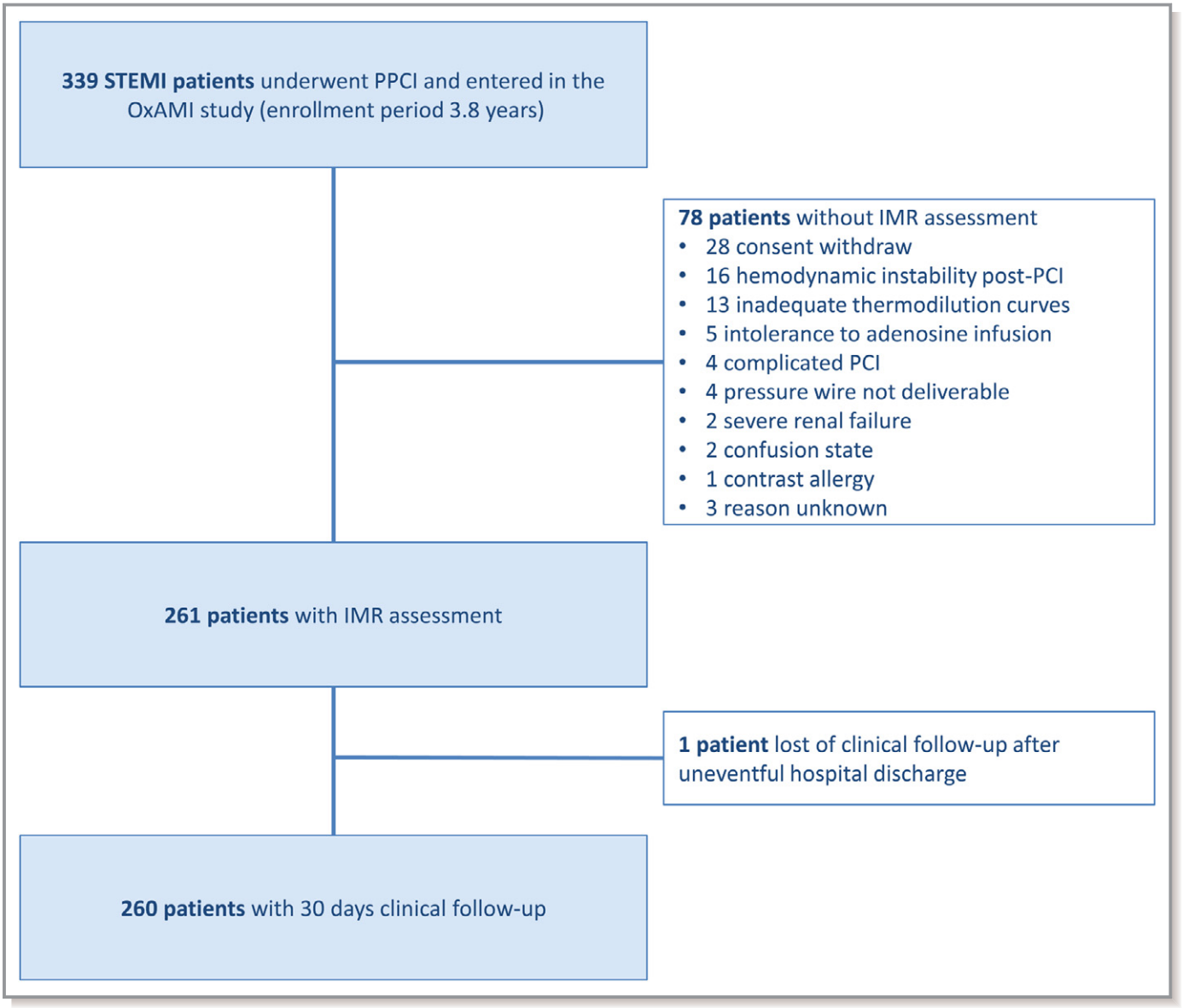


Figure 1. Study flowchart. IMR indicates index of microcirculatory resistance; OxAMI, Oxford Study in Acute Myocardial Infarction; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

hyperemic transit time, and fractional flow reserve was defined as the mean distal pressure divided by the mean proximal pressure during maximal hyperemia.

Clinical End Point and Follow-up

Major cardiac complications were defined as the following events after completion of the PPCI and at any time within 30 days: cardiac death (including sudden death), cardiogenic shock (prolonged hypotension with systolic blood pressure <90 mm Hg and signs of organ hypoperfusion requiring treatment), documented pulmonary edema (evidence of pulmonary congestion on chest radiographs, requirement for administration of intravenous diuretics, and impaired left ventricular function with ejection fraction ≤45% on transthoracic echocardiography), malignant ventricular tachycardia (ventricular fibrillation or sustained ventricular tachycardia requiring immediate defibrillation or cardioversion, respectively), malignant bradyarrhythmia (requiring administration of atropine or isoprenaline, and/or pacing), cardiac wall rupture, and intraventricular thrombus (revealed by echocardiography and/or cardiac magnetic resonance scan).

Data from 30-day clinical follow-up were collected by either telephone interview or office visit. All staff collating the outcome data was blinded to the coronary physiology data. One patient was lost to 30-day follow-up after an uneventful hospital discharge on day 3 and emigration at 10 days after PPCI, resulting in a total follow-up rate of 99.6%.

Guideline-Recommended Risk Scores

According to the PAMI-II criteria, low-risk patients are aged <70 years with a left ventricular ejection fraction >45%, 1- or 2-vessel disease, successful PCI (<50% residual stenosis and TIMI [Thrombolysis in Myocardial Infarction] flow grade ≥2 or 3), and no persistent arrhythmias.[17] The Zwolle score defines STEMI patients as low risk if they have ≤3 of 16 points based on Killip class, postprocedural TIMI flow, age <60 years, ischemic time <4 hours, and absence of 3-vessel disease or anterior myocardial infarction[18] (Table S1).

In the present study, experienced operators assessed pre- and postprocedural TIMI flow at angiography. Transthoracic echocardiography to obtain left ventricular function was performed before discharge by operators who were blinded to the coronary physiology indices.

Angiographic area at risk was assessed by the BARI (Bypass Angioplasty Revascularization Investigation) jeopardy score, as described previously.[13]

Statistical Analysis

Continuous variables are reported as mean±SD or median and interquartile range, as appropriate. Frequencies are given as absolute values and percentages. Normally distributed continuous variables (age, creatinine, heart rate, stent diameter) were compared using the unpaired *t* test. The Mann–Whitney *U* test was used to compare continuous variables that were not normally distributed. Comparisons between frequencies were performed using χ^2 statistics or the Fisher exact test. Kaplan–Meier methodology and the associated log-rank test were performed to determine the differences in 30-day major cardiac complication-free survival between the high and low IMR groups. The area derived from receiver operating characteristic curves was used to assess the performance of coronary physiology indices (IMR and CFR), and the previously validated PAMI-II and Zwolle scores were used to predict early major cardiac complications. The DeLong methodology[19] was chosen to compare the performance of the individual tests. All tests were 2-sided, and a $P<0.05$ was accepted as statistically significant. DeLong analysis was performed on MedCalc 16.4.1. All other statistical analyses were performed using SPSS version 22.0 (IBM Corp).

Results

Baseline Characteristics

A total of 261 patients presenting with STEMI for PPCI were prospectively enrolled in 3 sequential periods between October 2010 and December 2015 (Figure 1). The average age was 61.4 years, and 209 patients (80.0%) were male (Table 1). Overall, 112 patients (42.9%) presented with an anterior myocardial infarction, 24 (9.2%) were Killip class >1, and 17 (7.0%) had blood pressure <90 mm Hg on admission. Median pain-to-wire time was 3.0 hours (interquartile range: 2.1–5.0 hours), with a door-to-wire time of 20 minutes (interquartile range: 15.0–28.0 minutes). Most patients (86.4%) underwent PPCI via radial access. Intravenous adenosine was well tolerated by 98% of patients, and there were no adverse events related to the invasive coronary physiology measurements (Figure 1). In total, 22 major cardiac complications were documented in 17 of the 261 patients at 30 days (Table 2); all first events occurred during the index hospital admission.

Diagnostic Performance of IMR, CFR, and Risk Scores to Predict Clinical Outcome

According to the receiver operating characteristic curve analysis, IMR showed excellent performance to predict major cardiac complications, with an area under the curve (AUC) of 0.90 (95% confidence interval [CI], 0.85–0.93) and performed significantly better than CFR (AUC: 0.75; 95% CI, 0.69–0.80; $P=0.006$), the PAMI-II score (AUC: 0.71; 95% CI, 0.66–0.77; $P=0.001$), and the Zwolle score (AUC: 0.72; 95% CI, 0.66–0.77; $P=0.004$), as shown in Figure 2. Discriminative ability according to the AUC was similar for CFR and the PAMI-II and Zwolle scores.

According the established cutoff values,[12,17,18,20] IMR >40 was measured in 102 of 261 patients (39.1%) and was able to identify all 17 patients (sensitivity: 100%) with early major cardiac complications following an acute myocardial infarction, with a specificity of 65.2% (Figure 2). The individual complications are shown in Table 2. In patients with an adverse event, the IMR value was between 65 and 171 (median: 98.2; interquartile range: 87.2–114.8). As visualized on the receiver operating characteristic curve in Figure 2, an IMR cutoff value of 40 provides a sufficient safety margin before losing sensitivity of 100%. CFR stratified by a value of 2 and PAMI-II >0 achieved lower sensitivity (94.1% and 88.2%, respectively) and specificity (26.6% and 45.5%, respectively) compared with IMR >40 to identify patients developing an early complication (Figure 2). The sensitivity of the Zwolle score stratified by a value of 3 to predict a composite end point was lowest at 26.5%. The plots of continuous IMR, CFR, and PAMI-II and Zwolle scores against major cardiac complications are reported in Figure S1.

Outcome and Patient Characteristics Stratified by an IMR Value of 40

The percentage of patients free of major cardiac complications over time for the 2 IMR groups in a per-patient analysis is shown in Figure 3 (log-rank, $P<0.001$), with a divergence of the curves solely during the early course. Patients in the high-IMR group were characterized by older average age, more

Table 1. Clinical Characteristics on Admission Stratified by IMR

	Whole Cohort (N=261)	IMR ≤40 (n=159)	IMR >40 (n=102)	*P* Value
Male sex, n	209 (80.0)	130 (81.7)	79 (77.5)	0.40
Age, y, mean	61.4±12.0	59.4±11.8	64.5±11.6	0.001
Comorbidities, n				
Hypertension	100 (38.3)	54 (34.0)	46 (45.1)	0.07
Hypercholesterolemia	98 (37.5)	59 (37.1)	39 (38.2)	0.90
Diabetes mellitus	27 (10.3)	18 (11.3)	9 (8.8)	0.52
History of smoking	166 (63.6)	110 (69.2)	56 (54.9)	0.02
Family history of IHD	102 (39.1)	67 (42.1)	35 (34.3)	0.23
Creatinine, μmol/L, mean	81.2±25.7	80.3±25.6	81.8±26.2	0.74
Previous myocardial infarction	22 (8.5)	12 (7.6)	10 (10.0)	0.50
Periprocedural medications, n				
Aspirin	257 (98.5)	156 (98.1)	101 (99.0)	1.00
Clopidogrel	239 (91.6)	148 (93.1)	91 (89.2)	0.27
Ticagrelor/prasugrel	10 (3.8)	6 (3.8)	4 (3.9)	1.00
Thrombus aspiration	219 (83.9)	131 (82.4)	88 (86.3)	0.41
Beta blocker	36 (13.8)	19 (11.9)	17 (16.7)	0.28
ACE inhibitor	63 (24.1)	33 (20.8)	30 (29.4)	0.11
Clinical presentation, n				
Systolic blood pressure <90 mm Hg	17 (7.0)	11 (7.5)	6 (6.2)	0.70
Heart rate before PCI, beats/min, mean	79.5±17.0	79.6±17.1	79.3±17.0	0.89
Killip class >1	24 (9.2)	13 (8.2)	11 (10.8)	0.20
Pain-to-wire time, n				
<4 h	169 (64.8)	109 (68.6)	60 (58.8)	0.28
≥4 and <12 h	79 (30.3)	43 (27.0)	36 (35.3)	
≥12 h	13 (5.0)	7 (4.4)	6 (5.9)	
Pain-to-wire time, min, median	178.0 (126.5–298.0)	167.0 (125.0–256.0)	204.5 (127.3–339.0)	0.11
Door-to-wire time, min, median	20.0 (15.0–28.0)	20.0 (15.0–29.0)	18.0 (13.3–25.8)	0.20
Culprit vessel, n				
Left anterior descending	112 (42.9)	69 (43.4)	43 (42.2)	0.83
Left circumflex	27 (10.3)	15 (9.4)	12 (11.8)	
Right coronary artery	122 (46.7)	75 (47.2)	47 (46.1)	
BARI jeopardy score, median	30.8 (26.8–38.7)	31.0 (27.7–38.7)	29.8 (25.3–37.7)	0.61
Number of vessels with disease, n				
1	172 (65.9)	110 (69.2)	62 (60.8)	0.31
2	52 (19.9)	30 (18.9)	22 (21.6)	
3	37 (14.2)	19 (11.9)	18 (17.6)	
TIMI flow before PCI, n				
0/1	217 (83.1)	127 (79.9)	90 (88.2)	0.29
2	29 (11.1)	20 (12.6)	9 (8.8)	
3	12 (4.6)	9 (5.7)	3 (2.9)	

Continued

Table 1. Continued

	Whole Cohort (N=261)	IMR ≤40 (n=159)	IMR >40 (n=102)	*P* Value
TIMI flow after PCI, n				
0/1	2 (0.8)	0 (0.0)	2 (2.0)	0.02
2	25 (9.6)	10 (6.3)	15 (14.7)	
3	234 (89.7)	149 (93.7)	85 (83.3)	
Stent volume, mm^3, median	251.3 (188.5–365.6)	268.6 (192.4–352.0)	240.6 (173.2–457.7)	0.51
Stent diameter, mm	3.5 (3.5–4.0)	3.5 (3.5–4.0)	3.5 (3.4–4.0)	0.71
Stent length, mm	24.0 (18.0–36.0)	24.0 (18.0–33.0)	26.0 (18.0–38.0)	0.55
PAMI-II score >0, n	148 (56.7)	76 (47.8)	72 (70.6)	<0.001
Zwolle score >3, n	54 (20.7)	27 (17.0)	27 (26.5)	0.07
Coronary physiology, median				
IMR	32.3 (19.6–54.5)	21.4 (16.0–30.7)	69.8 (51.8–107.1)	<0.001
CFR	1.46 (1.08–1.92)	1.68 (1.28–2.24)	1.18 (0.92–1.50)	<0.001
FFR	0.93 (0.89–0.98)	0.92 (0.89–0.97)	0.94 (0.90–0.99)	0.01

Values are n (%), mean (±SD), or median (interquartile range). ACE indicates angiotensin-converting enzyme; BARI, Bypass Angioplasty Revascularization Investigation; CFR, coronary flow reserve; FFR, fractional flow reserve; IHD, ischemic heart disease; IMR, index of microcirculatory resistance; PAMI-II, Primary Angioplasty in Myocardial Infarction II; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

frequent history of smoking, more frequently impaired postprocedural TIMI flow, lower CFR, higher fractional flow reserve, and more frequently positive PAMI-II score (Table 1). Ischemic time, preprocedural TIMI flow, culprit vessel, BARI jeopardy score, and implanted stent volume did not significantly differ between the high- and low-IMR groups. Clinical characteristics at the time of discharge revealed that infarct size measured by troponin was larger, left ventricular ejection fraction was more often impaired, and more patients stayed in hospital longer than the median of 3 days in the high-IMR group than in the low-IMR group (Table 3).

Discussion

This study demonstrates that IMR measured at the time of PPCI for STEMI can independently select patients at very low risk of in-hospital cardiac complications and outperforms current guideline-recommended risk scores. These novel findings suggest that measuring IMR following PPCI may identify patients who could be triaged for less intensive nursing care and early discharge.

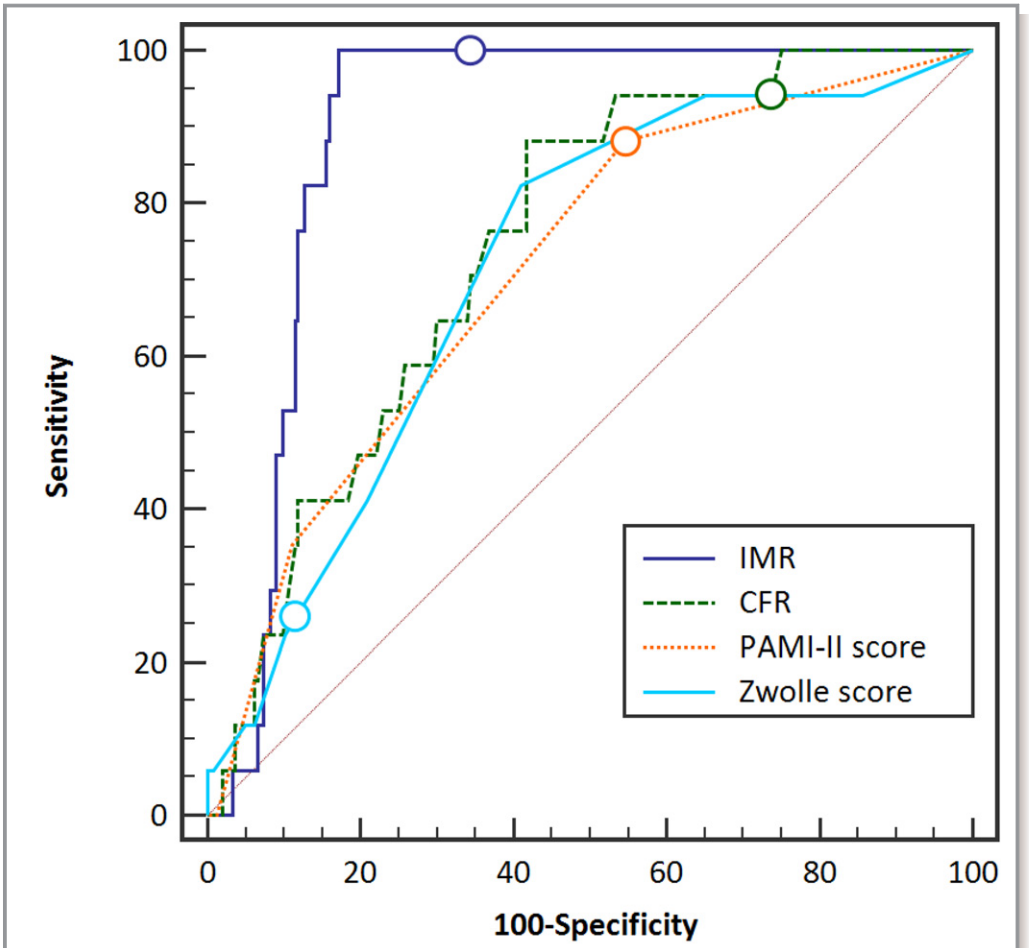
Risk Scores as Predictors of Early Major Cardiac Complications

The risk stratification of patients with an acute myocardial infarction has been a longstanding clinical challenge.[3,21] Current international guidelines suggest that PPCI patients with a "low-risk of complications" might be candidates for non-ICU admission[5] and early discharge[2] and mention the PAMI-II and Zwolle scores as useful risk-stratification tools.[17,18]

Table 2. Major Cardiac Complications at 30 Days Stratified by IMR

	Whole Cohort (N=261)	IMR ≤40 (n=159)	IMR >40 (n=102)	*P* Value
Major cardiac complications	17 (6.5)	0 (0.0)	17 (16.7)	<0.001
Cardiac death	2 (0.8)	0 (0.0)	2 (2.0)	0.15
Cardiogenic shock	3 (1.2)	0 (0.0)	3 (2.9)	0.06
Pulmonary edema	8 (3.1)	0 (0.0)	8 (7.8)	<0.001
Malignant ventricular tachyarrhythmia	4 (1.5)	0 (0.0)	4 (3.9)	0.02
Malignant bradyarrhythmia	1 (0.4)	0 (0.0)	1 (1.0)	0.39
Cardiac rupture	0 (0.0)	0 (0.0)	0 (0.0)	–
Intraventricular thrombus	4 (1.5)	0 (0.0)	4 (3.9)	0.02

Values are n (%). IMR indicates index of microcirculatory resistance.



	IMR	CFR	PAMI-II score	Zwolle score
AUC (95% CI)	0.90 (0.85 – 0.93)	0.75 (0.69 – 0.80)	0.71 (0.66 – 0.77)	0.72 (0.66 – 0.77)
	IMR > 40	CFR < 2	PAMI-II score > 0	Zwolle score > 3
Sens, % (95% CI)	100 (80.5 – 100)	94.1 (71.3 – 99.9)	88.2 (63.6 – 98.5)	26.5 (18.2 – 36.1)
Spec, % (95% CI)	65.2 (58.8 – 71.1)	26.6 (21.2 – 32.7)	45.5 (39.1 – 52.0)	83.0 (76.3 – 88.5)

Figure 2. Diagnostic value to predict early major cardiac complications. Comparison of receiver operating characteristic curves of individual tests to predict early major cardiac complications. IMR performed significantly better than CFR, PAMI-II, and Zwolle score (DeLong: *P*=0.006, *P*=0.001, and *P*=0.004, respectively). There was no difference among CFR, PAMI-II, and Zwolle score. Individual cutoff values are marked on the curves. AUC indicates area under the receiver operating characteristic curve; CFR, coronary flow reserve; CI, confidence interval; IMR, index of microcirculatory resistance; PAMI-II, Primary Angioplasty in Myocardial Infarction II; Sens, sensitivity; Spec, specificity.

In our cohort, the PAMI-II criteria identified 43% of patients as low risk but, importantly, misclassified 12% who developed a major cardiac complication during the hospital stay (AUC: 0.71). A Zwolle score ≤3 identified 79% as low-risk candidates, but more than two-thirds of in-hospital complications subsequently occurred in this group (AUC: 0.72).

Patients developing heart failure and ventricular arrhythmia after an acute myocardial infarction are discrete groups[22]: Acute severe heart failure, cardiac rupture, and intraventricular thrombus occur after extensive myocardial damage. Life-threatening ventricular arrhythmia during the early postinfarct phase in apparently stable patients is associated with ongoing ischemia,[23,24] making such adverse events difficult to predict. Ischemia may occur as a consequence of microvascular injury, despite restoring the flow in the epicardial coronary artery.[25] Angiographic parameters such as the TIMI flow grade

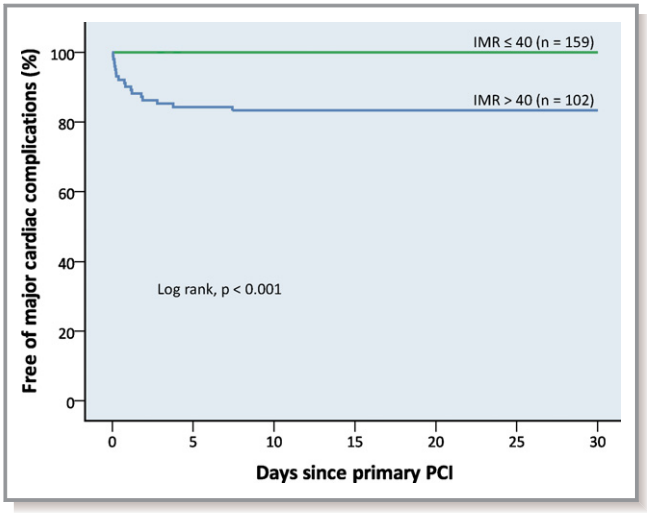


Figure 3. Free of major cardiac complications at 30 days. Kaplan–Meier curves comparing percentages of patients free of major cardiac complications at 30 days after primary PCI in groups with low (≤40) and high (>40) IMR. IMR indicates index of microcirculatory resistance; PCI, percutaneous coronary intervention.

(which is incorporated in the PAMI-II and Zwolle scores) and myocardial blush grade were widely accepted as semiquantitative measures of microvascular perfusion; however, it has become increasingly evident that angiographic perfusion characteristics alone do not reliably predict the occurrence of microvascular dysfunction.[26–28] Moreover, angiographic assessment of left ventricular ejection fraction at the time of PPCI (which is incorporated in the PAMI-II score) cannot differentiate between reversible stunning and irreversibly damaged myocardium, and the latter carries a higher risk for poor outcome. These limitations of angiographic assessment may in part account for the poor performance of the PAMI-II and Zwolle risk scores in predicting early major cardiac complications.

Microvascular Indices as Predictors of Early Major Cardiac Complications

IMR is an objective and specific index to assess the microcirculation, which can easily and safely be measured at the time of PPCI.[7,8] The strength of IMR is not only in predicting myocardial recovery, final infarct size, and left ventricular ejection fraction,[9–11] which are related to subsequent heart failure, but also in predicting the presence of microvascular dysfunction,[10,11] which is itself associated with early life-threatening ventricular arrhythmias.[29]

In our cohort, the lowest IMR value in a patient who developed an adverse event was 65. A cutoff value ≈64 would offer the highest specificity while still maintaining sensitivity of 100%. We appreciate that a cutoff value of 40 is rather conservative; however, misclassifying a patient may have important clinical consequences. To provide a clinical safety margin, we adopted the previously validated IMR threshold of 40 (which confers longer term prognostic value such as death and rehospitalization for heart failure[12]) and defined 159 of the 261 STEMI patients (61%) as low risk, allowing correct prediction of all 22 major cardiac complications in our sample.

The lower predictive value of CFR compared with IMR for early major cardiac complications was mainly driven by low specificity (26.6%) and low positive predictive value (8.2%). This maybe explained by the influence of hemodynamic factors, such as heart rate and blood pressure on CFR,[8] which have less impact on IMR. Furthermore, CFR is unable to distinguish between the contribution of epicardial and microvascular beds to total resistance.[7]

A prior study investigated whether microvascular dysfunction predicts in-hospital cardiac complications.[30] This study was limited to anterior acute myocardial infarction and used Doppler wire technology. Cardiac death or ventricular rupture occurred in 16 of the 169 patients and was reported only in the group with microvascular dysfunction. In that study, all types of ventricular tachyarrhythmia (including benign reperfusion arrhythmias and nonsustained ventricular tachycardia) and "protocol-defined" heart failure (including any type of dyspnea or Killip class >1) were reported more frequently in the group with severe microvascular dysfunction. These findings are in line with our results, but our study extends these observations to all territories, focuses on clinically relevant complications, and uses more accessible technology to measure microvascular dysfunction.

Table 3. Clinical Characteristics Before Discharge Stratified by IMR

	Whole Cohort (N=261)	IMR ≤40 (n=159)	IMR >40 (n=102)	*P* Value
Troponin peak, ng/mL	77.5 (30.8–176.0)	54.7 (25.7–143.1)	120.5 (42.0–293.1)	0.01
Troponin AUC	107.4 (45.6–292.1)	89.5 (35.3–259.3)	131.7 (52.3–409.4)	0.02
LVEF ≤45%	86 (33.0)	41 (25.8)	45 (44.1)	0.002
In-hospital stay >3 days	53 (20.3)	26 (16.4)	27 (26.5)	0.04

Values are n (%) or median (interquartile range). AUC indicates area under the curve; IMR, index of microcirculatory resistance; LVEF, left ventricular ejection fraction.

Furthermore, our study extends the original report of the utility of IMR measured at PPCI to identify a high-risk group.[12] In that study, the adverse outcomes of patients with an IMR >40 continued to be poorer, with ongoing separation of the Kaplan–Meier curves out to 3-year follow-up, but no analysis of the early time point was conducted. We suggest that a significant number of adverse events occur very early in that group and may be a target for closer monitoring and treatment while allowing those with very low early risk to be triaged.

Clinical Implications

IMR <40 following PPCI predicts uneventful in-hospital recovery, providing a basis to investigate whether this low-risk group may be safely managed in a lower monitoring environment. This information is available at the time of completing the PPCI and may apply to ≈60% of STEMI patients, based on our cohort, and would have major implications on the ICU admission rate.[31] In addition, this approach may improve patient experience[32] and shorten the overall hospital stay by facilitating early discharge, with consequent reduction in hospital costs.[17,18] Furthermore, those patients with an IMR >40 represent a group at very high risk of early in-hospital complications and may benefit from even more intensive monitoring.

Limitations

Several limitations must be taken into account when interpreting our results. First, this is a single-center observational cohort study. Nevertheless, our cohort of 261 compares well in size with the original study reporting the long-term prognostic value of IMR in 253 patients.[12] Second, the 6.5% rate of in-hospital major cardiac complications in our study is lower than reported in registry data. Coronary physiology measurements were undertaken if there were no safety or clinical concerns, and that causes a selection bias toward lower risk patients. The rate of in-hospital cardiac complications in the 78 patients without coronary physiology measurements was 14.1% (cardiac death, 2.6%; cardiogenic shock, 1.3%; pulmonary edema, 5.1%; malignant ventricular tachyarrhythmia, 5.1%; malignant bradyarrhythmia, 2.6%; intraventricular thrombus, 1.3%). Sixteen of these patients (20.5%) were hemodynamically unstable following PPCI and would have been judged as high risk at the outset. In 13 patients (16.6%), IMR could not be calculated because of nonmeasurable transit times. A detailed list of excluded patients is available in Figure 1. These limitations do not allow generalization to all STEMI patients; however, they may strengthen the potential value of our findings because IMR reliably identified the low-risk patients in an already preselected lowest risk group. A comprehensive analysis in a clinical prospective all-comers cohort is needed, but clinician recognition that the patient is too sick for this assessment appears in itself to be an important marker of risk.

The safety, feasibility, efficacy, and economic analysis of using IMR obtained at the time of PPCI to allow very early identification of high- and low-risk patients and the subsequent implications for where and how they are managed based on an IMR strategy requires prospective validation.

Conclusion

Coronary guidewire-based assessment of IMR immediately at the end of PPCI for STEMI reliably predicted early cardiac complications and outperformed current guideline-recommended strategies in terms of risk stratification. These novel findings provide evidence to test IMR as a tool to identify low-risk patients, who may not require admission to an ICU and are candidates for early discharge, and high-risk patients, who may need more intensive treatment.

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Disclosures

None.

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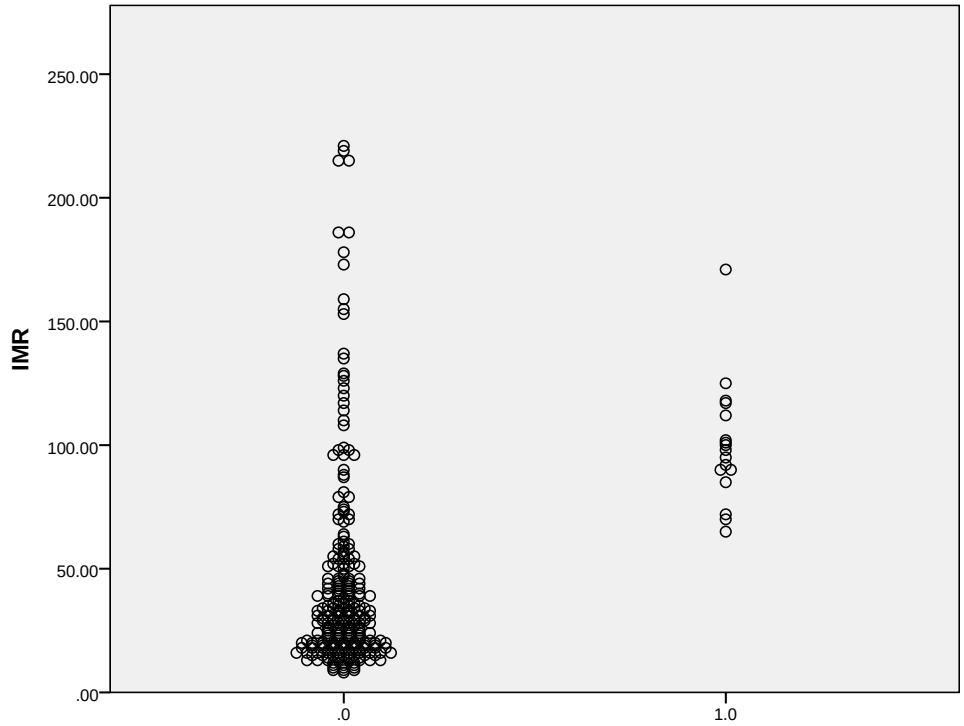
SUPPLEMENTAL MATERIAL

Table S1. Guideline-recommended Risk Scores for ST-segment Elevation Myocardial Infarction

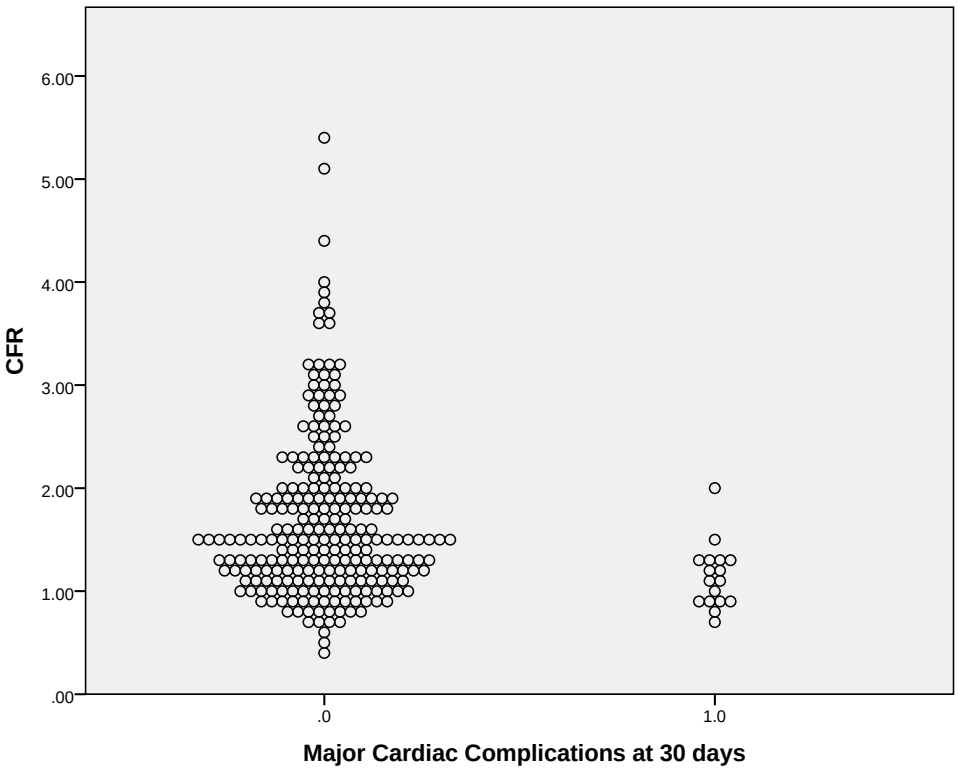
PAMI-II Risk Score		Zwolle Risk Score	
Age	**Points**	**Age**	**Points**
≤ 70	0	< 60	0
> 70	1	≥ 60	2
LVEF		**Killip Class**	
> 45%	0	1	0
≤ 45%	1	2	4
		3-4	9
3-vessel disease		**3-vessel disease**	
No	0	No	0
Yes	1	Yes	1
TIMI flow post		**TIMI flow post**	
2 or 3	0	3	0
0 or 1	1	2	1
		0 or 1	2
Persistent arrhythmias		**Anterior infarction**	
No	0	No	0
Yes	1	Yes	1
Residual stenosis		**Ischemic time (> 4 h)**	
< 50%	0	No	0
≥ 50%	1	Yes	1
Low Risk if	**0**	**Low Risk if**	**≤ 3**

(LVEF: Left Ventricular Ejection Fraction, TIMI: Thrombolysis In Myocardial Infarction)

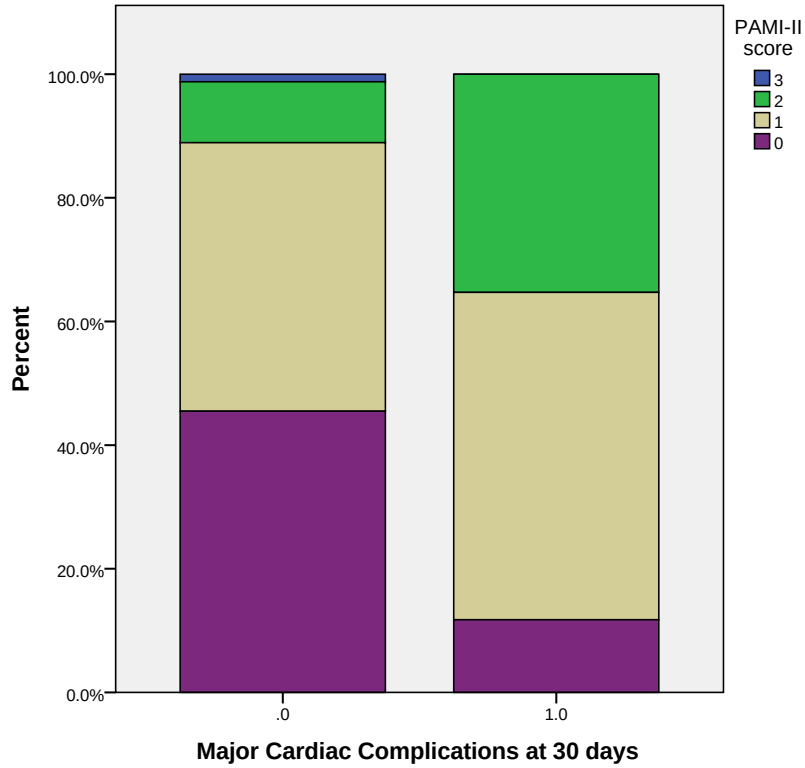
Figure S1. Scatter Plot of IMR (A) and CFR (B) and Mosaic Plot of PAMI-II (C) and Zwolle score (D) against Major Cardiac Complications at 30 Days



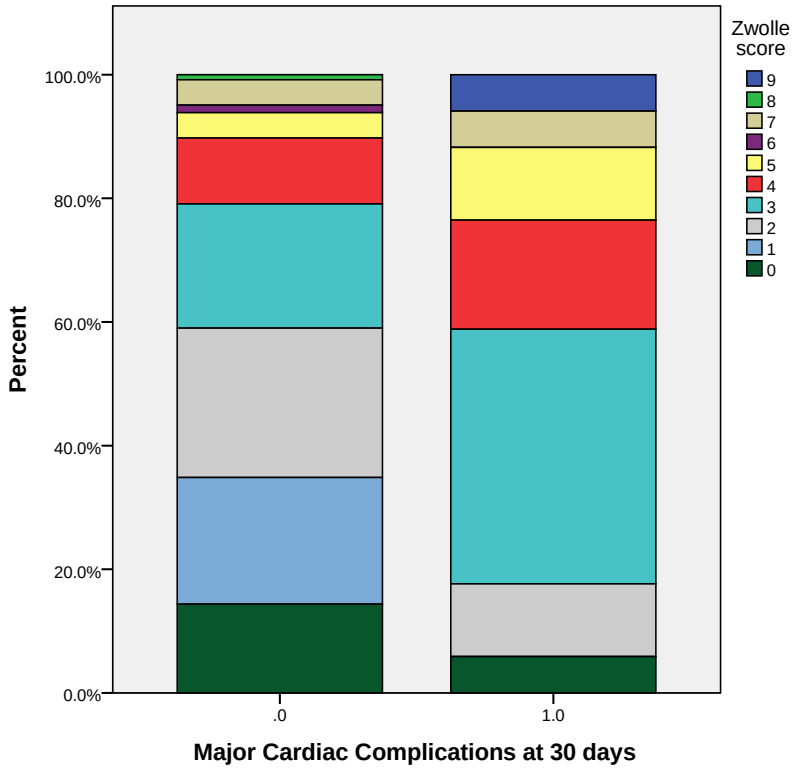
A



B


PAMI-II score
3
2
1
0
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
Percent
.0
1.0
Major Cardiac Complications at 30 days

C


Zwolle score
9
8
7
6
5
4
3
2
1
0
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
Percent
.0
1.0
Major Cardiac Complications at 30 days

D