CJC Open 6 (2024) 122–132

Original Article

Management and Outcomes of Type I and Type II Myocardial Infarction in Cardiogenic Shock

Cameron Stotts, BSc,[a,b,c,‡] Richard G. Jung, MD, PhD,[a,b,d,‡] Graeme Prosperi-Porta, MD,[a,e] Pietro Di Santo, MD,[a,e,f] Omar Abdel-Razek, MD,[a,e] Simon Parlow, MD,[a,e] F. Daniel Ramirez, MD, MSc,[a,e] Trevor Simard, MD,[g] Marino Labinaz, MD,[e] Baylie Morgan, RN,[a] Lisa Robinson, RN,[a] Rebecca Mathew, MD,[a,e] and Benjamin Hibbert, MD, PhD[a,b,d,g]

[a] *CAPITAL Research Group, University of Ottawa Heart Institute, Ottawa, Ontario, Canada*

[b] *Vascular Biology and Experimental Medicine Laboratory, University of Ottawa Heart Institute, Ottawa, Ontario, Canada*

[c] *Department of Biochemistry, Microbiology, and Immunology, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada*

[d] *Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada*

[e] *Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada*

[f] *School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada*

[g] *Mayo Clinic, Rochester, Minnesota, USA*

ABSTRACT

Background: Type I myocardial infarction (T1MI) or type II myocardial infarction (T2MI) have different underlying mechanisms; however, in the setting of cardiogenic shock (CS), it is not understood if patients experience resultantly different outcomes. The objective of this study was to determine clinical features, biomarker patterns, and outcomes in these subgroups.

Methods: Patients from the CAPITAL-DOREMI trial presenting with acute myocardial infarction-associated CS (n = 103) were classified as T1MI (n = 61) or T2MI (n = 42). The primary endpoint was a composite of all-cause in-hospital mortality, cardiac arrest, the need for mechanical circulatory support, or initiation of renal replacement therapy

RÉSUMÉ

Introduction : L'infarctus du myocarde de type 1 (IMT1) et l'infarctus du myocarde de type 2 (IMT2) ont des mécanismes sous-jacents différents. Toutefois, dans le contexte du choc cardiogénique (CC), nous ignorons si les patients ont donc des résultats cliniques différents. Les objectifs de la présente étude étaient de déterminer les caractéristiques cliniques, les profils des biomarqueurs et les résultats cliniques dans ces sous-groupes.

Méthodes : Les patients de l'essai CAPITAL-DOREMI qui présentaient un CC associé à un infarctus aigu du myocarde (n = 103) étaient classifiés dans le sous-groupe IMT1 (n = 61) ou dans le sous-groupe IMT2 (n = 42). Le critère de jugement principal était un critère com-

Cardiogenic shock (CS) is defined as a state of inadequate cardiac output that results in end-organ hypoperfusion. The prognosis of patients with CS is poor and often results in a mortality rate ranging from 30% to 60%.[1] To date, early revascularization, specifically of the culprit lesion, is the most well-recognized therapeutic approach to improve short-term survival in patients with CS.[2-7] Other treatments for the initial management and hemodynamic stabilization of CS involves the use of inotropes, vasopressors, and mechanical circulatory support (MCS). To evaluate the efficacy of inotrope use, the CAPITAL-DOREMI trial [**Ca**rdiovascular **P**ercutaneous **I**ntervention **Tri**al Group (CAPITAL)-**Do**butamine Compa**re**d to **Mi**lrinone (DOREMI); ClinicalTrials.gov Identifier NCT03207165] randomized patients with CS to receive either milrinone or dobutamine (1:1) inotropic therapies and evaluated the impact on clinical outcomes.[8]

In-hospital mortality in patients with CS remains high, with most registries reporting rates between 30% and 40%.[9,10] Approximately 30% to 80% of CS cases are related to acute myocardial infarction (MI),[10,11] which is classified as being developed from atherosclerotic plaque disruption of epicardial coronary arteries, type I, or caused by oxygen supply and

Received for publication June 5, 2023. Accepted October 11, 2023.

‡These authors contributed equally to this work.

Corresponding author: Dr Benjamin Hibbert, Department of Cardiovascular Medicine, Interventional Cardiology and Critical Care Cardiology, Mayo Clinic, 200 First Street, Rochester, Minnesota, USA. Tel.: 1 507 255 5846.

E-mail: Hibbert.Benjamin@mayo.edu

Twitter: @benhibbertMDPhD

See page 132 for disclosure information.

https://doi.org/10.1016/j.cjco.2023.10.011

at 30 days. Secondary endpoints were evaluated as individual components of the primary endpoint.

Results: Patients with T1MI CS did not have a higher incidence of the primary composite endpoint compared with T2MI CS (adjusted hazard ratio [HR], 1.63; 95% confidence interval [CI], 0.96-2.77; $P = 0.07$). Cardiac biomarkers including troponin I ($P < 0.001$), and creatine kinase levels ($P = 0.001$) were elevated in patients with T1MI CS compared with T2MI. Furthermore, patients with T1MI CS presented with decreased urine output ($P = 0.01$) compared with T2MI. Predictors of T2MI CS included nonischemic ventricular dysfunction ($P = 0.002$), atrial fibrillation ($P = 0.02$), and chronic obstructive pulmonary disease ($P = 0.002$).

Conclusions: There were no differences in adverse clinical outcomes between patients with T1MI and T2MI CS, although the events were numerically increased, and the sample size was small. Overall, this study provides a hypothesis-generating analysis regarding the clinical and biochemical outcomes in T1MI vs T2MI CS.

posite qui regroupait la mortalité à l'hôpital toutes causes confondues, l'arrêt cardiaque, la nécessité d'une assistance circulatoire mécanique ou l'amorce d'une thérapie de remplacement rénal dans les 30 jours. Les critères secondaires étaient évalués en fonction des composantes individuelles du critère de jugement principal.

Résultats : Les patients qui avaient un CC-IMT1 n'avaient pas une plus grande fréquence de survenue du critère de jugement principal composite que les patients qui avaient un CC-IMT2 (rapport de risque [RR] ajusté, 1,63 ; intervalle de confiance [IC] à 95 %, 0,96-2,77 ; $P = 0,07$). Les biomarqueurs cardiaques dont les concentrations de la troponine I ($P < 0,001$) et de la créatine kinase ($P = 0,001$) étaient élevées chez les patients qui avaient un CC-IMT1, mais non chez les patients qui avaient un CC-IMT2. De plus, les patients qui avaient eu un CC-IMT1 avaient une diurèse réduite ($P = 0,01$), mais non les patients qui avaient un CC-IMT2. Les prédicteurs du CC-IMT2 étaient la dysfonction ventriculaire non ischémique ($P = 0,002$), la fibrillation auriculaire ($P = 0,02$) et la maladie pulmonaire obstructive chronique ($P = 0,002$).

Conclusions : Il n'y avait aucune différence dans les résultats cliniques défavorables entre les patients qui avaient un CC-IMT1 et les patients qui avaient un CC-IMT2, bien que les événements aient augmenté en nombre, et que la taille de l'échantillon était petite. Dans l'ensemble, cette étude fournit une analyse de génération d'hypothèses quant aux résultats cliniques et biochimiques du CC-IMT1 *vs* du CC-IMT2.

demand mismatch, type II.[12,13] Outside the setting of CS, there are distinct differences in the clinical severity and outcomes in patients with type I myocardial infarction (T1MI) and type II myocardial infarction (T2MI). Specifically, T2MI is associated with higher in-patient, 30-day, and 1-year mortality compared with T1MI,[14-17] which, in part, can be attributed to the higher prevalence of comorbidities including chronic kidney disease and heart failure.[18] Regardless, most clinical studies to date do not differentiate among patients based on the etiology of acute myocardial infarction complicated by CS (AMICS). Further information regarding the stratification of patients with CS from T1MI and T2MI origination will allow for improved monitoring practices and the adjustment to therapeutic strategies, depending on the origin of AMICS manifestation.

Given the lack of comparative data between T1MI and T2MI etiologies of CS, the objective of this study was to perform a hypothesis-generating analysis to evaluate differences in clinical and biochemical outcomes between these subgroups of the DOREMI randomized trial. We further elaborate on modifiable and nonmodifiable risk factors associated with the development of T2MI etiology of CS compared with T1MI.

Methods

Study design

This study is a post hoc analysis of the DOREMI trial, a double-blind randomized clinical trial comparing the impact of dobutamine or milrinone on the outcomes of patients with CS.[8] This study was approved by the Ottawa Health Science Network Research Ethics Board and conducted in accordance with the Helsinki Declaration. Written informed consent was received from all eligible participants or the substitute decision maker before randomization. All data sets and analyses performed in this study are available from the corresponding author on reasonable request.

Full details of the CAPITAL-DOREMI trial are previously described.[8] In brief, patients with acute coronary syndrome and complicated by CS were randomized (1:1) to receive either dobutamine or milrinone. Inclusion criteria included adult patients (> 18 years of age) admitted with Society for Cardiovascular Angiography and Interventions (SCAI) stages B to E CS, according to currently accepted guidelines[19] between September 1, 2017, and May 17, 2020, and met an indication for inotrope therapy: (1) a clinical diagnosis of CS with a blood pressure < 90 mm Hg with indications of end-organ hypoperfusion; (2) evidence of systemic or pulmonary congestion despite use of vasodilators or diuretics; (3) acute coronary syndrome complicated by CS with hemodynamic reduction in cardiac index (< 1.8 L/min per m^2 and left ventricular end-diastolic pressure > 18 mm Hg); (4) clinical need to increase cardiac output in combination with ongoing vasopressor therapy; and (5) the treating team's assessment that inotrope therapy is needed for developing CS despite the absence of end-organ hypoperfusion. Patients were excluded from the study if presenting with out-of-hospital cardiac arrest, were pregnant, initiation of inotrope treatment before enrollment, participating in another interventional trial, deemed ineligible by the treating physician, or informed consent was not obtained from the patient or substitute decision maker. In this substudy, the primary analysis was performed in patients with measured troponin I levels and excluded those who had troponin T levels measured (introduced to the Ottawa region on November 27, 2019).

Endpoint analysis

Patients with AMICS with either T1MI or T2MI etiology according to the Fourth Universal Definition of Myocardial

Infarction (UDMI)[12] were included in the DOREMI trial. The complete 4th UDMI criteria for adjudication of T1MI or T2MI are described in Supplemental Table S1. Briefly, T1MI was defined as caused by atherosclerotic plaque rupture or erosion with a change in cardiac troponin levels with 1 of the following: new ischemic changes by electrocardiogram, symptoms of acute myocardial ischemia, myocardial damage as assessed by troponin elevation, or development of abnormal Q wave. T2MI was defined as the mismatch between oxygen supply and demand without acute coronary atherothrombosis, changes in cardiac troponin levels, and 1 of the following: new ischemic changes by electrocardiogram, symptoms of acute myocardial ischemia, myocardial damage as assessed by troponin elevation, abnormal Q wave development, tachyarrhythmias, hypertension, bradyarrhythmia, respiratory failure, severe anemia, vasospasm, arterial dissection, or fixed coronary artery disease (CAD). Classification of type of MI was made independently from the presentation diagnosis through review of the medical record by a cardiologist blinded to treatment assignment and outcome.[20]

The inclusion criteria for this post hoc analysis were identical to the original DOREMI study. Patients with acute myocardial injury secondary to cardiogenic shock without evidence of MI were excluded. The primary endpoint of this analysis was defined as the composite of all-cause mortality, nonfatal MI, requirement of mechanical circulatory support or cardiac transplant, resuscitated cardiac arrest, or initiation of renal replacement therapy at 30 days. Secondary endpoints included the individual components of the primary endpoints, with the addition of total length of stay in hospital, total time on inotropes, number of days in the cardiac intensive care unit, and the number of patients requiring invasive or noninvasive mechanical ventilation. Moreover, hemodynamic changes—including heart rate, mean arterial pressure, vasoactive-ionotropic score, and hourly urine output in addition to biochemical parameters including serum creatinine, sodium, potassium, troponin, and creatine kinase levels—were evaluated.

Statistical analysis

This subgroup analysis represents a post hoc analysis of the DOREMI trial. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) and evaluated using Student's *t*-test or Mann-Whitney U test. Categorical variables are summarized as number (percentage) and evaluating using χ^2 test or Fisher's exact test. Hazard ratios (HRs) were calculated by Cox proportional hazards model and presented as HR and 95% confidence interval (CI). Univariable logistic regression analysis was performed to determine variables for inclusion in the multivariable model using a cut-off of $P < 0.20$. Variables that reached statistical significance included age $\geq$ 75, female sex, left ventricular ejection fraction, nonischemic ventricular dysfunction, previous MI, atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), diabetes, and troponin I > 5 upper limit of normal (ULN). The Youden Index was performed to determine the optimal cut-off value for cardiac troponin I (cTnI) levels.[21] Data analysis was performed using SAS v9.4 (SAS Institute, Cary, NC), and all figures were created using GraphPad Prism v8 (GraphPad Software, La Jolla, CA).

Results

Baseline and procedural characteristics

A total of 319 patients were screened at our institution from September 1, 2017, to May 17, 2020. Overall, 192 eligible patients were enrolled in the study and randomized 1:1 to milrinone or dobutamine. Of these, 168 (87.5%) patients had troponin I levels measured at the time of enrollment. MI classification was performed by a cardiologist through review of the medical records rather than the presentation diagnosis; therefore, classifications will differ from previous analyses from our group.[20] In total, 103 patients were included in the study following removal of patients with acute myocardial injury as the etiology of CS and patients without clinical evidence of MI. After adjudication, 61 (59%) were diagnosed with T1MI, and 42 (41%) were diagnosed with T2MI secondary to CS (Fig. 1). Further details on patient enrollment and treatment procedures are included in the original DOREMI publication.[8]

The baseline characteristics of the study population are listed in Table 1. The mean age of patients with T1MI and T2MI were 72.5 ± 11.6 and 71.3 ± 11.9, respectively. The number of female patients in each group was 15 (25%) in T1MI and 17 (41%) in T2MI. Coronary angiography was performed in 58 (95%) of patients with T1MI CS and 20 of 41 (49%) of patients with T2MI CS. More patients in the T1MI CS group (n = 46, 75%) underwent percutaneous coronary intervention compared with T2MI CS (n = 6, 14%). There were no noteworthy differences among groups according to the SCAI CS class, in addition to comorbidities including chronic kidney disease, COPD, hypertension, dyslipidemia, active smoker, and previous cardiac procedures or events such as MI, stroke, percutaneous coronary intervention, and coronary artery bypass graft. Presentation of atrial fibrillation at baseline assessment was higher in the T2MI group compared with the T1MI group with 25 (60%) and 14 (23%), respectively. Medications received by patients with T1MI and T2MI CS 24 hours before randomization varied slightly including aspirin, P2Y12 inhibitor, warfarin, beta blocker, mineralocorticoid receptor antagonist, diuretic, and amiodarone. The etiologies of T2MI CS included chronic ischemic cardiomyopathy (33%), stenosis or regurgitation (21%), arrhythmias (19%), nonischemic cardiomyopathy (10%), infection and sepsis (5%), other (5%), or unknown (7%). Baseline characteristics of excluded patients with troponin T levels measured at the time of admission with T1MI or T2MI CS (n = 15) are reported in Supplemental Table S2.

Clinical outcomes

T1MI was not statistically associated with an increase in the primary composite outcome compared with T2MI (unadjusted HR, 1.62; 95% CI, 0.96-2.74; $P = 0.07$; Table 2) and when adjusted for age and sex (adjusted HR, 1.63; 95% CI, 0.96-2.77; $P = 0.07$; Fig. 2A); however, numerically, the

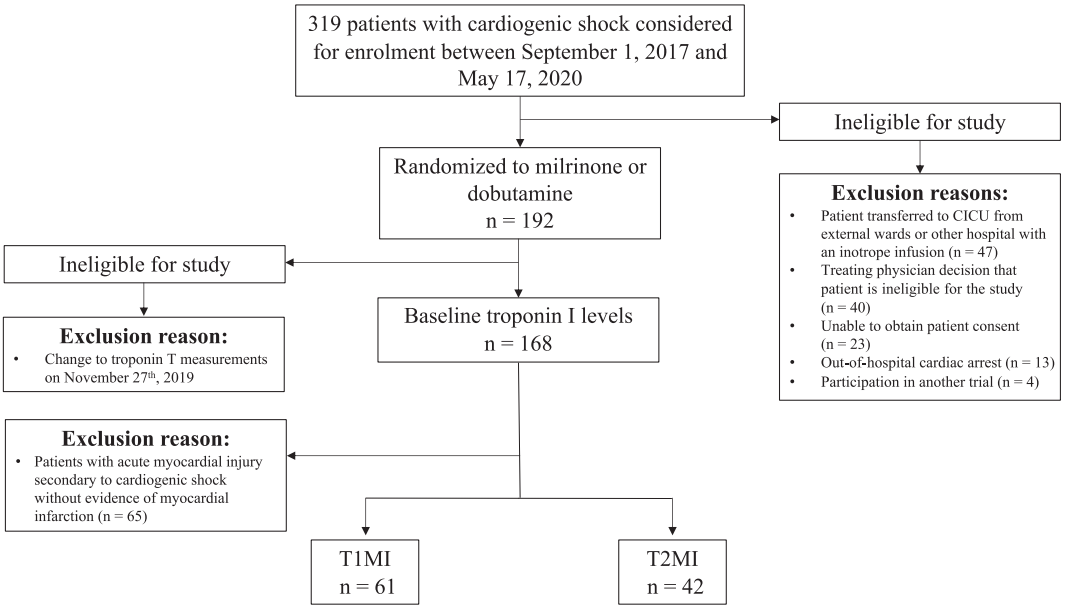

Figure 1. Study flow diagram. Flow diagram of total patients screened at our institution, ineligible patients, randomization 1:1 to dobutamine or milrinone, and etiology of cardiogenic shock (CS). CICU, cardiac intensive care unit.

primary endpoint was higher in patients with T1MI CS. Initiation of renal replacement therapy did not differ between patients with T1MI and T2MI etiologies of CS (adjusted HR, 2.05; 95% CI, 0.79-5.31; $P = 0.14$; Fig. 2B). In addition, there was no statistical difference in all-cause mortality in patients with T1MI (49%) compared with T2MI (41%) CS (adjusted HR, 1.28; 95% CI, 0.70-2.34; $P = 0.43$; Fig. 2C). No statistical differences were observed between the 2 groups in terms of the incidence of resuscitated cardiac arrest and transient ischemic attack or stroke.

Numerically, patients with T1MI CS experienced a lower median number of days of hospital length of stay compared with patients with T2MI CS; however, this association was not statistically significant (10.0 [4.0-21.0] days vs 19.5 [9.0-28.0] days, respectively; $P = 0.056$; Table 2). No statistical differences were observed in median number of days of cardiac intensive care unit length of stay (7.0 [6.0-9.0] days vs 7.0 [4.0-9.0] days; $P = 0.62$; Table 2) and median number of total time on inotropes (88 [38.0-168.0] hours vs 92.5 [20.0-168.0] hours; $P = 0.58$; Table 2) in T1MI and T2MI, respectively. Moreover, no noticeable differences in the number of patients requiring noninvasive or invasive mechanical ventilation after randomization were observed across both groups. Primary and secondary outcomes in patients with only troponin T levels measured at the time of admission with T1MI and T2MI CS are reported in Supplemental Table S3.

Biochemical and hemodynamic parameters

Important biochemical and hemodynamic parameters were collected from baseline to 120 hours in both groups. Elevated troponin I levels were observed in patients with T1MI compared with T2MI CS ($P < 0.001$; Fig. 3A). In addition, patients with T1MI presented with higher creatine kinase levels compared with T2MI ($P = 0.001$; Fig. 3B). No statistical differences in other hemodynamic and biochemical parameters were observed between T1MI and T2MI etiologies of CS, including heart rate, mean arterial pressure, vasoactive-inotrope score, and lactate levels (Fig. 3, C-F).

Renal outcomes

Impaired renal function was observed in patients with T1MI etiology of CS compared with T2MI with respect to urine output ($P = 0.01$; Fig. 4A). There was no statistical difference in creatinine levels between groups ($P = 0.93$; Fig. 4B).

Factors associated with the development of T2MI CS

Univariable logistic regression demonstrated age ≥ 75 ($P = 0.11$), female sex ($P = 0.09$), decreased left ventricular ejection fraction ($P = 0.12$), nonischemic ventricular dysfunction ($P < 0.001$), previous MI ($P = 0.13$), AF ($P < 0.001$), COPD ($P = 0.18$), diabetes ($P = 0.02$), and troponin I > 5 ULN ($P < 0.001$) to be associated with the incidence of T2MI CS compared with T1MI CS (Supplemental Table S4). Variables with $P < 0.20$ were included in a forward model of multivariable logistic regression, which identified nonischemic ventricular dysfunction ($P = 0.002$), AF ($P = 0.02$), and COPD ($P = 0.002$) as being associated with the development of T2MI CS compared with T1MI CS (Table 3).

The univariate regression analysis identified that cTnI levels > 5, > 10, > 15, > 20 ULN (ng/mL) was associated with a reduced risk in the development of T2MI compared with T1MI CS (Supplemental Table S4). Although troponin I levels have been shown not to distinguish between T1MI and T2MI in patients without CS,[22] this has not been validated in the setting of CS. For better interpretation of the results, we

Table 1. Baseline characteristics

	T1MI (n = 61)	T2MI (n = 42)	*P* value
Age, years, mean ± SD	72.5 (± 11.6)	71.3 (± 11.9)	0.57
Female patients: number (%)	15 (25)	17 (40)	0.09
Body mass index, median [IQR]	26.2 [22.9-30.7]	25.6 [22.3-32.0]	0.70
Inotrope: number (%)			0.22
Milrinone	26 (43)	23 (55)	
Dobutamine	35 (57)	19 (45)	
LVEF, median [IQR]	27.0 [21.0-45.0]	25.0 [20.0-38.0]	0.1
Creatinine, median [IQR: μmol/L]	137.0 [97.0-182.0]	107.0 [71.0-123.0]	0.08
Etiology of ventricular dysfunction			0.49
Ischemic	28 (48)	17 (41)	
Nonischemic	31 (53)	25 (60)	
Comorbidities			
Previous MI	20 (33)	20 (48)	0.13
Previous PCI	19 (31)	10 (24)	0.42
Previous coronary artery bypass grafting	11 (18)	9 (21)	0.67
Previous stroke/transient ischemic attack	8 (13)	4 (10)	0.58
Atrial fibrillation	14 (23)	25 (60)	0.0002
Chronic kidney disease	14 (23)	8 (19)	0.63
Chronic obstructive pulmonary disease	8 (13)	2 (5)	0.16
Hypertension	39 (64)	29 (69)	0.59
Diabetes	22 (37)	25 (60)	0.02
Dyslipidemia	34 (56)	25 (60)	0.70
Active smoker	8 (13)	8 (19)	0.41
Medications received in 24 hours before randomization: number (%)			
Aspirin	56 (92)	26 (62)	0.0002
P2Y12 inhibitor	55 (90)	21 (50)	< 0.0001
Warfarin	1 (2)	4 (10)	0.07
Direct oral anticoagulant	8 (13)	9 (21)	0.26
Statin	45 (74)	28 (67)	0.44
Beta blocker	19 (31)	21 (50)	0.054
ACE inhibitor, ARB, or angiotensin receptor neprilysin inhibitor	21 (34)	18 (43)	0.39
Mineralocorticoid receptor antagonist	4 (7)	6 (14)	0.19
Nitrates/hydralazine	8 (13)	9 (21)	0.26
Diuretic	41 (67)	36 (86)	0.03
Digoxin	2 (3)	3 (7)	0.37
Amiodarone	11 (18)	21 (50)	0.0006
SCAI cardiogenic shock class: number (%)			
Class B	3 (5)	2 (5)	0.97
Class C	48 (79)	33 (79)	0.99
Class D	9 (15)	4 (10)	0.43
Class E	1 (2)	3 (7)	0.16
Invasive hemodynamics, median [IQR] (n = 19)			
Cardiac index	1.70 [1.65-2.07]	2.11 [2.06-2.15]	0.78
Systolic PAP	39.5 [34.5-42.5]	44.0 [36.0-58.0]	0.39
Diastolic PAP	22.0 [15.5-24.0]	23.0 [20.5-28.0]	0.44
Mean PAP	29.0 [27.0-42.0]	28.5 [26.0-39.5]	0.84
Central venous pressure	13.5 [11.0-14.5]	13.0 [12.0-14.0]	0.72
Pulmonary capillary wedge pressure	24.0 [19.0-29.0]	24.0 [20.0-28.0]	1.00
Systemic vascular resistance	1872.5 [1324.0-2052.0]	1614.5 [1195.0-1840.0]	0.32
Pulmonary vascular resistance	283.5 [171.0-417.5]	116.0 [79.0-170.0]	0.08
PCI performed	46 (75)	6 (14)	< 0.0001
Coronary angiogram performed	58 (95)	20 of 41 (49)	< 0.0001
Vasopressor: number (%)	37 (61)	18 (43)	0.08
Intra-aortic balloon pump: number (%)	9 (15)	1 (2)	0.04
Ventilation: number (%)			0.25
Noninvasive	5 (8)	3 (7)	
Invasive	22 (36)	9 (25)	
Etiology of T2MI			
Infection/sepsis		2 (5)	
Chronic ischemic cardiomyopathy		14 (33)	
Nonischemic cardiomyopathy		4 (10)	
Arrythmias		8 (19)	
Stenosis or regurgitation		9 (21)	

Table 1. Continued.

	T1MI (n = 61)	T2MI (n = 42)	*P* value
Other		2 (5)	
Unknown		3 (7)	
Values are reported as number (%) or median [IQR]			

ACE, angiotensin converting enzyme; ARB, angiotensin-II receptor blocker; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAP, pulmonary artery pressure; PCI, percutaneous coronary intervention; SD, standard deviation; T1MI, type I MI; SCAI, Society for Cardiovascular Angiography and Interventions; T2MI, type II MI.

have reported the optimal cut-off point (Youden Index) for delta TnI for T1MI vs T2MI CS. The optimal cut-off point (Youden Index) was identified as delta TnI > 1193.58 ng/mL (n = 50). Troponin I difference using this cut-off was associated with the development of T1MI CS (odds ratio [OR], 27.99; 95% CI, 6.50-80.58; $P < 0.01$); Supplemental Table S5).

Discussion

In this post hoc analysis of the DOREMI trial, we sought to compare outcomes in patients with T1MI and T2MI etiologies of CS. Herein, we did not demonstrate more frequent clinical events in patients with T1MI CS, although these were numerically more frequent, and our sample size was small. Although there was no difference between several biochemical and hemodynamic factors, troponin I levels were significantly elevated in patients with T1MI compared with T2MI CS. In addition, patients with T1MI CS displayed impaired renal function, including decreased urine output compared with T2MI CS. Finally, we identified risk factors for the development of T2MI etiology of CS that included nonischemic ventricular dysfunction, AF, and COPD.

To our knowledge, this is the first study that stratifies outcomes following CS based on type of MI. Outside the setting of CS, studies comparing mortality rates in patients with T1MI and T2MI are controversial. Specifically, the **Ca**theter **Sa**mpled **Bl**ood Archive i**n Ca**rdiovascular Diseases (CASABLANCA) study reports no change in the mortality rate of patients with T1MI compared with T2MI[23]; however, other studies demonstrate T2MI is associated with a 3-fold increase in in-hospital and 30-day mortality compared with T1MI.[14] In the setting of CS, our study reports no difference in all-cause mortality between T1MI and T2MI etiologies of

Table 2. Primary and secondary outcomes

			T1MI vs T2MI			
Outcome	T1MI (n = 61)	T2MI (n = 42)	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Primary outcome, n (%)						
Composite of all-cause mortality, resuscitated cardiac arrest, need for MCS or cardiac transplant, nonfatal MI, TIA or stroke, or initiation of renal replacement therapy at 30 days	41 (67)	22 (52)	1.62 (0.96-2.74)	0.07	1.63 (0.96-2.77)	0.07
Secondary outcomes, n (%)						
Initiation of renal replacement therapy	16 (26)	6 (14)	2.10 (0.82-5.38)	0.12	2.05 (0.79-5.31)	0.14
All-cause mortality	30 (49)	17 (41)	1.40 (0.77-2.55)	0.27	1.28 (0.70-2.34)	0.43
Resuscitated cardiac arrest	7 (12)	5 (12)	1.05 (0.33-3.30)	0.94	0.93 (0.29-2.97)	0.90
Need for MCS or cardiac transplant	13 (21)	5 (12)	1.95 (0.70-5.48)	0.20	1.97 (0.68-5.72)	0.21
TIA or stroke	2 (3)	0 (0.0)	N/A	N/A	N/A	N/A
Median number of days of cardiac intensive care unit length of stay	7.0 [6.0-9.0]	7.0 [4.0-9.0]				
Median number of days of hospital length of stay	10.0 [4.0-21.0]	19.5 [9.0-28.0]				
Median number of hours of total time on inotropes	88.00 [38.0-168.0]	92.5 [20.0-168.0]				
Number of patients requiring noninvasive or invasive mechanical ventilation after randomization only	4 (7)	2 (5)				

Values are reported as number (%) or median [IQR]. All analyses performed using the intention-to-treat principle.

Adjusted for age, sex.

CI, confidence interval; HR, hazard ratio; MCS, mechanical circulatory support; MI, myocardial infarction; TIA, transient ischemic attack; T1MI, type I MI; T2MI, type II MI.

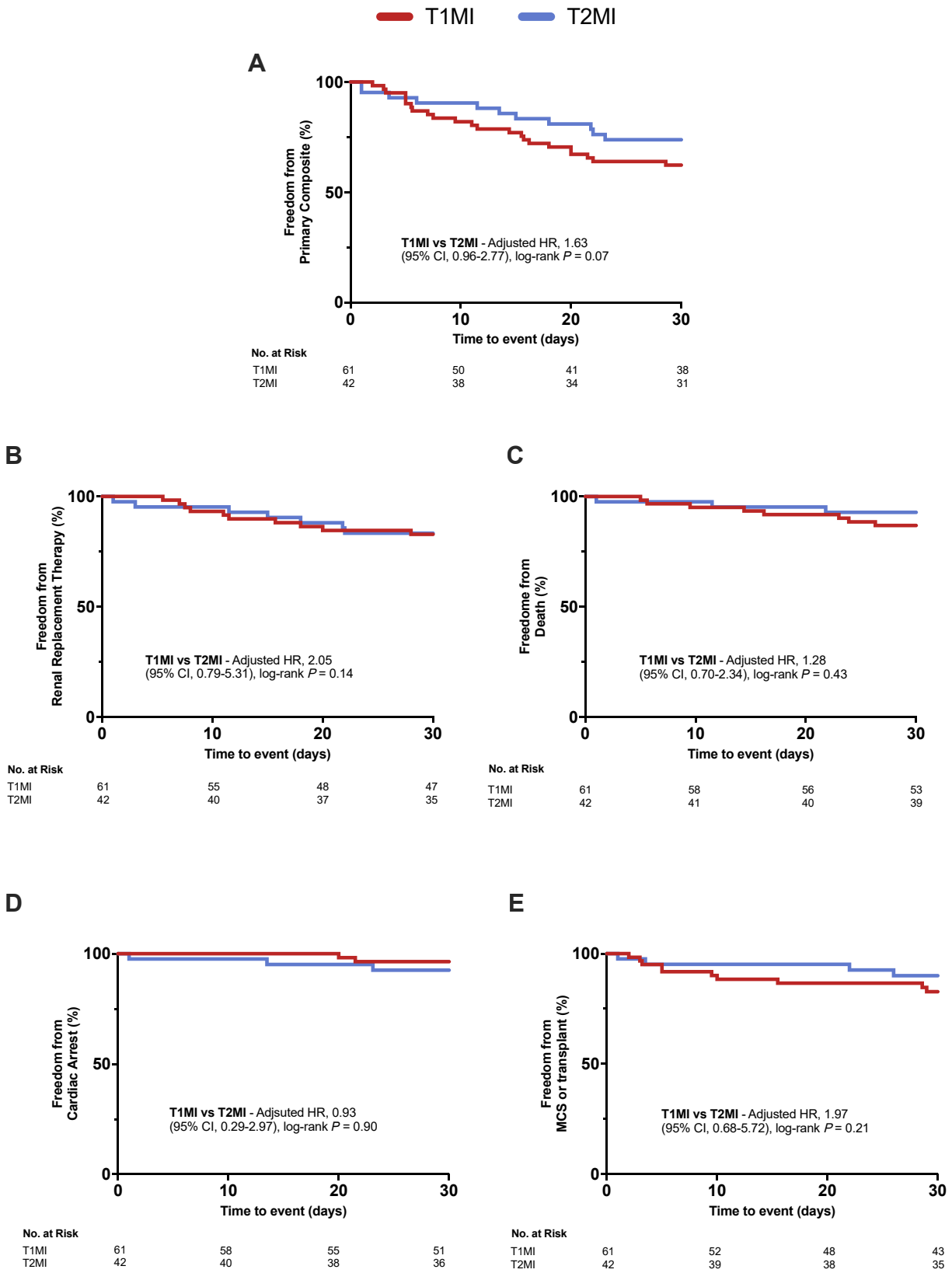

Figure 2. Kaplan-Meier estimates of patients stratified by T1MI and T2MI etiologies of CS presenting with primary and secondary endpoints. (**A**) There was no difference in the primary composite endpoint between T1MI and T2MI etiologies of CS (adjusted HR, 1.63; 95% CI, 0.96-2.77; $P = 0.07$). (**B**) No difference in the initiation of renal replacement therapy was observed in T1MI vs T2MI (adjusted HR, 2.05; 95% CI, 0.79-5.31; $P = 0.14$). (**C**) No difference was observed between both groups with respect to all-cause death (adjusted HR, 1.28; 95% CI, 0.70-2.34; $P = 0.43$).

CS. These results may be explained by the high mortality rate typically observed in patients with CS, therefore potentially masking differences in all-cause mortality between patients with T1MI or T2MI CS. Future studies will be needed to further delineate the risk of all-cause mortality between these groups.

Evaluation of biochemical parameter may help to delineate between T1MI or T2MI etiologies of CS and provide important information for physicians. cTnI is released into circulation during myocardial ischemia and infarction. TnIs are elevated in both T1MI and T2MI and is therefore used to aid in the diagnosis of acute MI.[24,25] No information exists for delineating predictive factors of T1MI etiology of CS in comparison with T2MI using cTnI levels; however, delta cTnI levels have been shown not to distinguish between T1MI and T2MI in patients without CS.[22] Herein, we demonstrate that in patients with CS, cTnI levels > 5, > 10, > 15, > 20 ULN (ng/mL), and a cut-off of delta TnI $>$ 1193.58 ng/mL were associated with the development of T1MI compared with T2MI CS. Feasibility of delineation between T1M1 and T2MI in CS may be possible because of the high severity of cardiac tissue damage, therefore allowing for a larger stratification among cTnI levels in various CS etiologies. For this reason, in the context of CS, cTnI levels may provide additional information regarding predictive factors for T1MI etiology of CS, therefore allowing for additional monitoring and treatment adjustments in this elevated at-risk patient population.

Delineating between patients with T2MI and T1MI is challenging and requires careful clinical assessment. Even after the incorporation of the 4th UDMI in 2018, the classification of T2MI and T1MI varies widely in clinical practice and studies. Further understanding of the patient and procedural risk factors associated with the development of T2MI compared with T1MI may help differentiate between these 2 etiologies of acute MI. Herein, we demonstrate that nonischemic ventricular dysfunction, AF, and COPD were associated with the development of T2MI compared with T1MI CS. To our knowledge, nonischemic ventricular dysfunction is not known to be associated with the development of T2MI CS; however, it is possible that the reduced heart function may result in the oxygen supply and demand mismatch that triggers T2MI. Similarly, it is possible that the association between COPD and T2MI CS arises because of the hypoxic state in this patient population.[26] Furthermore, outside the setting of CS, AF is a leading trigger of T2MI[27] and is more common in patients with T2MI compared with T1MI.[28] This aligns with our analysis evaluating risk factors associated with T2MI within the context of CS. Overall, this study is among the first to evaluate risk factors associated with the development of T2MI CS compared with T1MI CS. As this is a hypothesis-generating study, future cohorts will be needed before its incorporation into clinical practice.

In this study, we observed differences in renal function between T1MI and T2MI CS. As the kidneys receive approximately 25% of cardiac output, renal function is highly susceptible to end-organ hypoperfusion in CS.[29] Signs of cardiogenic shock specifically resulting from renal dysfunction include hyperkalemia, described as potassium levels ≥ 6 mmol/L, and oliguria, defined as urine output < 0.5 mL/kg/h.[30,31] Urine output in all groups remain in the normal range; however, patients with T1MI etiology of CS had reduced urine output compared with T2MI CS. Urine output as a marker for renal dysfunction in patients with T1MI CS was not accompanied by an increase in the initiation of renal replacement therapy compared with T2MI CS. Regardless, this study provides evidence that patients with T1MI CS may be more susceptible to end-organ renal dysfunction compared with T2MI CS, and increased monitoring of hemodynamic variables could be considered.

Limitations

First, the sample size of the overall DOREMI trial may not be sufficiently powered to determine differences in clinical events between the T1MI and T2MI subgroups. Specifically—although we report that there is no difference in the primary outcome—there remains a strong trend toward worse outcomes in patients with T1MI compared with T2MI CS. Future studies with a larger sample size are needed to further elucidate the differences in outcomes between T1MI and T2MI CS. Second, this study is a post hoc adjudication study; however, patient diagnoses and outcome measurements were performed by a cardiologist according to the 4th UDMI. Third, it is possible that patients categorized as T2MI CS had occult plaque rupture and were wrongly classified. Fourth, the DOREMI trial collected information on in-hospital outcomes only; therefore, this study is not able to provide data on the long-term outcomes between T1MI and T2MI CS, if present. Fifth, most participants in the DOREMI trial presented with Society for Cardiovascular Angiography and Interventions (SCAI) CS stage C. Sixth, it is possible that other etiologies of cardiorenal syndrome, including elevated central venous pressure and neurohormonal dysregulation, may have contributed to the reduced cardiac output in patients with CS and the subsequent primary cause of renal dysfunction, which was not discussed in our analysis. Seventh, the sample size of participants with an incidence of transient ischemic attack or stroke was minimal.

Overall, this study demonstrated distinct clinical features and biomarker patterns between patients with T1MI and T2MI CS. The elevated markers of myonecrosis and impaired renal function in patients with T1MI CS compared with T2MI CS provide insight into the possible need to adjust monitoring practices and therapeutic strategies based on manifestation of AMICS. However, more in depth analyses will be needed to determine if other etiologies of cardiorenal syndrome contribute to renal dysfunction in patients with CS.

Figure 2. *(continued)*

(**D**) No difference in the incidence of cardiac arrest was observed with T1MI vs T2MI (adjusted HR, 0.93; 95% CI, 0.29-2.97; $P = 0.90$). (**E**) No relationship existed in freedom from use of MCS or transplantation between T1MI and T2MI (adjusted HR, 1.97; 95% CI, 0.68-5.72; $P = 0.21$). CI, confidence interval; CS, cardiogenic shock; HR, hazard ratio; MCS, mechanical circulatory support; T1MI, type I myocardial infarction; T2MI, type II myocardial infarction.

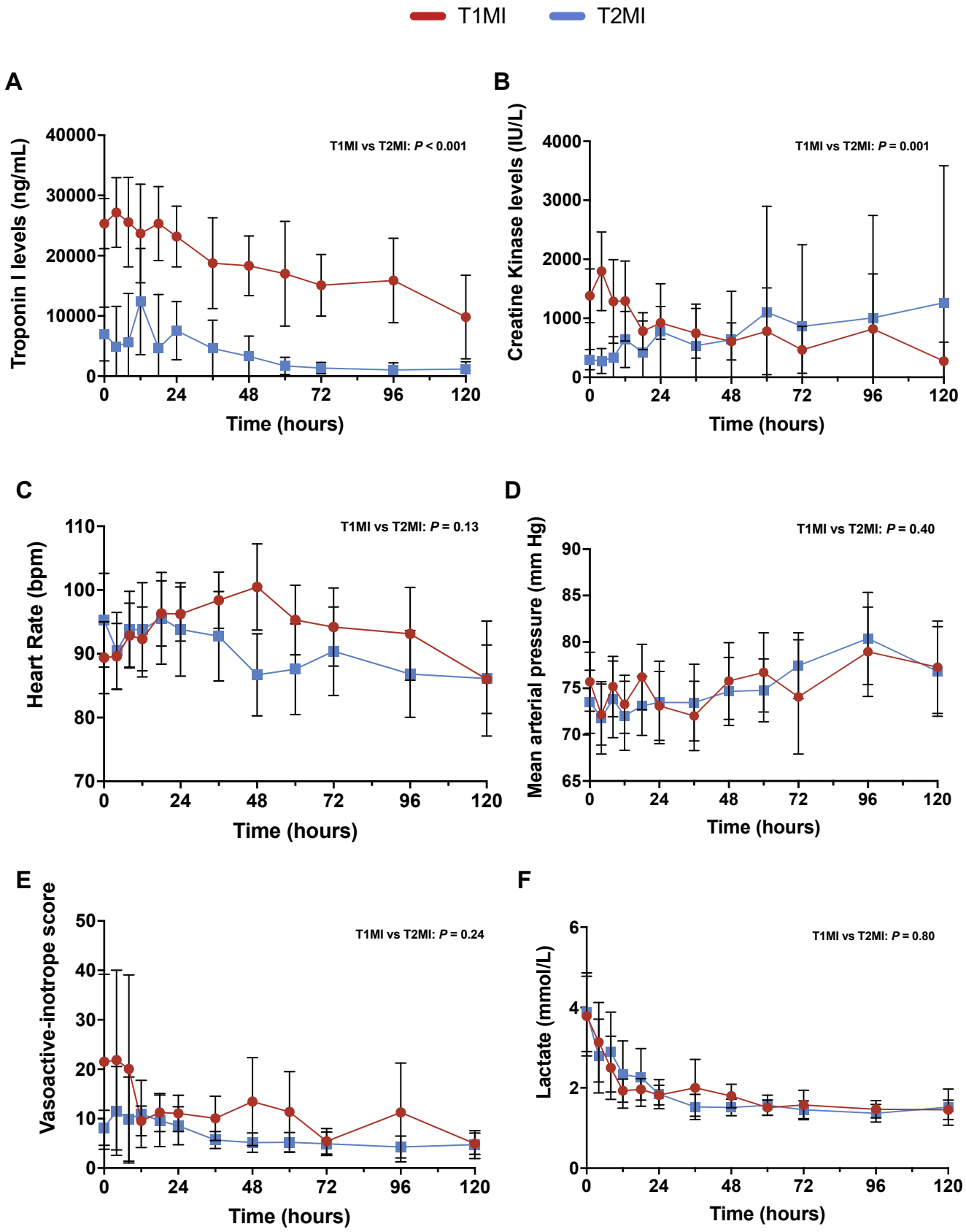

Figure 3. Changes in biochemical and hemodynamic parameters from baseline to 120 hours between T1MI and T2MI etiologies of CS. (**A**) Troponin T (ng/mL; $P < 0.001$). (**B**) Creatine kinase (IU/L; $P = 0.001$). (**C**) Heart rate (bpm; $P = 0.128$). (**D**) Mean arterial pressure (mm Hg; $P = 0.40$). (**E**) Vasoactive-inotrope score ($P = 0.24$). (**F**) Lactate (mmol/L; $P = 0.80$). A repeated measure mixed model was used to measure the continuous variables between T1MI and T2MI etiologies of CS. All panels are expressed as mean ± 95% CI. bpm, beats per minute; CI, confidence interval; CS, cardiogenic shock; T1MI, type I myocardial infarction; T2MI, type II myocardial infarction.

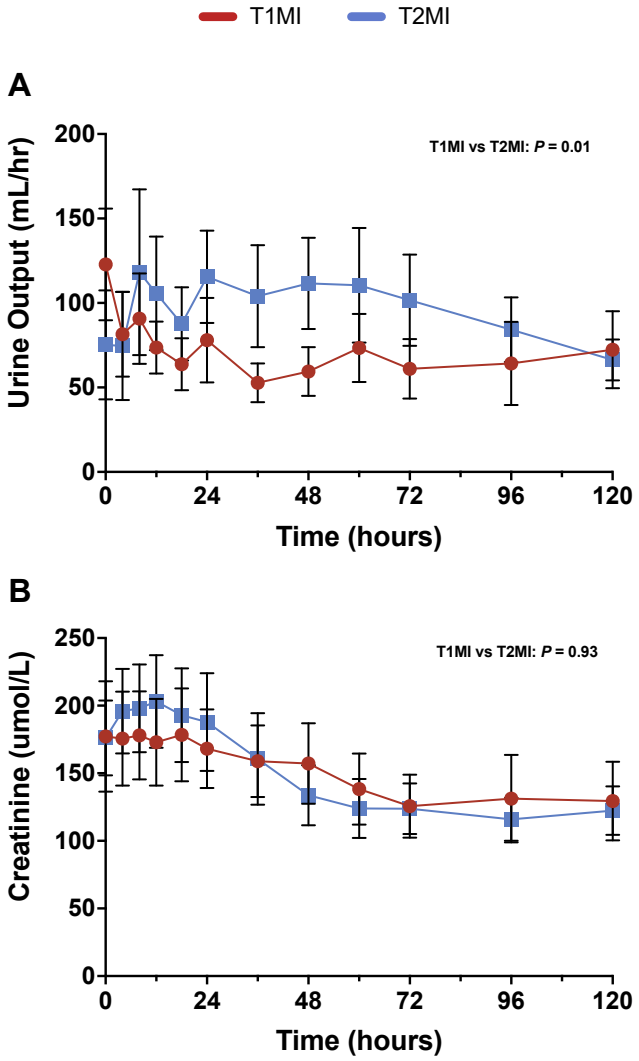

Figure 4. Changes in renal endpoints from baseline to 120 hours. (**A**) Urine output (mL/h) was reduced in patients with T1MI compared with T2MI ($P = 0.01$). (**B**) No change in creatinine levels (μmol/L; $P = 0.93$). A repeated measure mixed model was used to measure the continuous variables between T1MI and T2MI etiologies of CS. All panels are expressed as mean ± 95% CI. CI, confidence interval; CS, cardiogenic shock; T1MI, type I myocardial infarction; T2MI, type II myocardial infarction.

Furthermore, this study emphasises the need for delineation between T1MI or T2MI etiology of CS in future clinical trials to inform clinicians regarding risk stratification in these patient populations.

Table 3. Multivariable logistic regression for factors associated with the development of T2MI CS compared with T1MI CS

Variable	OR	95% CI		*P* value
Nonischemic ventricular dysfunction	38.054	3.817	379.398	0.002
Atrial fibrillation	3.906	1.22	12.504	0.02
Previous MI	0.079	0.01	0.622	0.02
COPD	6.744	1.98	22.967	0.002
C-statistic	0.85			
n	89			

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CS, cardiogenic shock; C-statistic, concordance statistic; MI, myocardial infarction; OR, odds ratio; T1MI, type I MI; T2MI, type II MI.

Conclusions

T1MI etiology of CS was not statistically associated with an increase in adverse clinical events compared with T2MI; however, there was a numerical increase in the frequency of events. Nonetheless, patients with T1MI vs T2MI CS displayed elevated markers of myonecrosis and impaired renal function. Finally, nonischemic ventricular dysfunction, AF, and COPD were associated with the development of T2MI etiology of CS compared with T1MI.

Ethics Statement

This study was approved by the Ottawa Health Science Network Research Ethics Board and was performed in accordance with the Helsinki Declaration.

Patient Consent

The authors confirm that a patient consent form(s) has been obtained for this article.

Funding Sources

No funding was provided for this article.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. van Diepen S, Katz JN, Albert NM, et al. contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 2017;136:e232-68.
2. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295:2511-5.
3. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. N Engl J Med 1999:341625-34.
4. Alexander JH, Reynolds HR, Stebbins AL, et al; TRIUMPH Investigators. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. JAMA 2007;297:1657-66.
5. Thiele H, Akin I, Sandri M, et al. One-year outcomes after PCI strategies in cardiogenic shock. N Engl J Med 2018;379:1699-710.
6. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017;377:2419-32.
7. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287-96.
8. Mathew R, Di Santo P, Jung RG, et al. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. N Engl J Med 2021;385:516-25.
9. Berg DD, Bohula EA, van Diepen S, et al. epidemiology of shock in contemporary cardiac intensive care units. Circ Cardiovasc Qual Outcomes 2019;12:e005618.
10. Berg DD, Bohula EA, Morrow DA. Epidemiology and causes of cardiogenic shock. Curr Opin Crit Care 2021;27:401-8.
11. Harjola VP, Lassus J, Sionis A, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail 2015;17:501-9.
12. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circulation 2018;138:e618-51.
13. Vahdatpour C, Collins D, Goldberg S. Cardiogenic shock. J Am Heart Assoc 2019;8:e011991.
14. Gupta S, Vaidya SR, Arora S, Bahekar A, Devarapally SR. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. Cardiovasc Diagn Ther 2017;7:348-58.
15. Lopez-Cuenca A, Gomez-Molina M, Flores-Blanco PJ, et al. Comparison between type-2 and type-1 myocardial infarction: clinical features, treatment strategies and outcomes. J Geriatr Cardiol 2016;13:15-22.
16. Sandoval Y, Smith SW, Sexter A, et al. Type 1 and 2 myocardial infarction and myocardial injury: clinical transition to high-sensitivity cardiac troponin I. Am J Med 2017;130:1431-1439.e4.
17. Singh A, Gupta A, DeFilippis EM, et al. Cardiovascular mortality after type 1 and type 2 myocardial infarction in young adults. J Am Coll Cardiol 2020;75:1003-13.
18. White K, Kinarivala M, Scott I. Diagnostic features, management and prognosis of type 2 myocardial infarction compared to type 1 myocardial infarction: a systematic review and meta-analysis. BMJ Open 2022;12:e055755.
19. Naidu SS, Baran DA, Jentzer JC, et al. SCAI SHOCK Stage Classification Expert Consensus Update: A Review and Incorporation of Validation Studies: This statement was endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) in December 2021. J Am Coll Cardiol 2022;79:933-46.
20. Jung RG, Di Santo P, Mathew R, et al. Implications of myocardial infarction on management and outcome in cardiogenic shock. J Am Heart Assoc 2021;10:e021570.
21. Ruopp MD, Perkins NJ, Whitcomb BW, Schisterman EF. Youden Index and optimal cut-point estimated from observations affected by a lower limit of detection. Biom J 2008;50:419-30.
22. Sandoval Y, Thordsen SE, Smith SW, et al. Cardiac troponin changes to distinguish type 1 and type 2 myocardial infarction and 180-day mortality risk. Eur Heart J Acute Cardiovasc Care 2014;3:317-25.
23. Gaggin HK, Liu Y, Lyass A, et al. incident type 2 myocardial infarction in a cohort of patients undergoing coronary or peripheral arterial angiography. Circulation 2017;135:116-27.
24. Eggers KM, Jaffe AS, Lind L, Venge P, Lindahl B. Value of cardiac troponin I cutoff concentrations below the 99th percentile for clinical decision-making. Clin Chem 2009;55:85-92.
25. Sandoval Y, Gunsolus IL, Smith SW, et al. Appropriateness of cardiac troponin testing: insights from the Use of TROPonin In Acute coronary syndromes (UTROPIA) Study. Am J Med 2019;132:869-74.
26. McAllister DA, Maclay JD, Mills NL, et al. Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. Eur Respir J 2012;39:1097-103.
27. Belkouche A, Yao H, Putot A, et al. The multifaceted interplay between atrial fibrillation and myocardial infarction: a review. J Clin Med 2021;10:198.
28. Putot A, Monin A, Belkouche A, Chague F, Zeller M, Cottin Y. Pre-existing atrial fibrillation and myocardial infarction: only 10% of infarcts directly linked to atrial fibrillation. Cardiovasc Endocrinol Metab 2022;11:e0267.
29. Lassus J. Kidney and liver dysfunction in cardiogenic shock. Curr Opin Crit Care 2020;26:417-23.
30. Tarvasmaki T, Haapio M, Mebazaa A, et al. Acute kidney injury in cardiogenic shock: definitions, incidence, haemodynamic alterations, and mortality. Eur J Heart Fail 2018;20:572-81.
31. Grodzinsky A, Goyal A, Gosch K, et al. Prevalence and prognosis of hyperkalemia in patients with acute myocardial infarction. Am J Med 2016;129:858-65.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.jcjopen.ca/ and at https://doi.org/10.1016/j.cjco.2023.10.011.