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Published in:
JOURNAL OF CARDIAC FAILURE

DOI:
[10.1016/j.cardfail.2021.01.006](https://doi.org/10.1016/j.cardfail.2021.01.006)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Perez, A. L., Grodin, J. L., Chaikijurajai, T., Wu, Y., Hernandez, A. F., Butler, J., Metra, M., Felker, G. M., Voors, A. A., McMurray, J. J., Armstrong, P. W., O'Connor, C., Starling, R. C., & Tang, W. H. W. (2021). Interleukin-6 and Outcomes in Acute Heart Failure: An ASCEND-HF Substudy. *JOURNAL OF CARDIAC FAILURE*, 27(6), 670-676. <https://doi.org/10.1016/j.cardfail.2021.01.006>

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Interleukin-6 and Outcomes in Acute Heart Failure: An ASCEND-HF Substudy

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ABSTRACT

Background: The inflammatory cytokine IL-6 has been previously implicated in the pathophysiology of acute decompensated heart failure (HF). Prior observations in acute HF patients have suggested that IL-6 may be associated with outcomes and modulated by nesiritide. We aimed to evaluate the associations between serial IL-6 measurements, mortality and rehospitalization in acute HF.

Methods and Results: We analyzed the associations between IL-6 in acute HF, readmission, and mortality (30 and 180 days) using a cohort of 883 hospitalized patients from the ASCEND-HF trial (nesiritide vs placebo). Plasma IL-6 was measured at randomization (baseline), 48–72 hours, and 30 days. The median IL-6 was highest at baseline (14.1 pg/mL) and decreased at subsequent time points (7.6 pg/mL at 30 days). In a univariable Cox regression analysis, the baseline IL-6 was associated with 30- and 180-day mortality (hazard ratio per log 1.74, 95% confidence interval 1.09–2.78, $P = .021$; hazard ratio 3.23, confidence interval 1.18–8.86, $P = .022$, respectively). However, there was no association after multivariable adjustment. IL-6 at 48–72 hours was found to be independently associated with 30-day mortality (hazard ratio 8.2, confidence interval 1.2–57.5, $P = .03$), but not 180-day mortality in multivariable analysis that included the ASCEND-HF risk model and amino terminal pro-B-type natriuretic peptide as covariates. In comparison with placebo, nesiritide therapy was not associated with differences in serial IL-6 levels.

Conclusions: Although elevated IL-6 levels were associated with higher all-cause mortality in acute HF, no independent association with this outcome was identified at baseline or 30-day measurements. In contrast with prior reports, we did not observe any impact of nesiritide over placebo on serial IL-6 levels. (*J Cardiac Fail* 2021;27:670–676)

Inflammation, a normal immune system response to stress, is a key factor in the development and progression of heart failure (HF).^{1,2} IL-6 is an important proinflammatory cytokine associated with HF and produced by T-helper 2 cells, affecting myocytes through IL-6 receptor (IL-6R) and gp130 signaling pathway.^{3–6} IL-6 signaling leads to decline in myocardial contractility by up-regulating myocardial

nitric oxide synthase⁷ and down-regulating the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2).⁸ In chronic HF, IL-6 tracks with disease severity and is an independent predictor of mortality.^{9–13} In acute HF, prior studies have suggested a prognostic association between IL-6 and adverse clinical outcomes.^{14–18} We sought to investigate the associations between serial assessments of plasma IL-6, mortality

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Manuscript received October 2, 2020; revised manuscript received December 21, 2020; revised manuscript accepted January 7, 2021.

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The ASCEND-HF study, including the biomarker substudy, was funded by Scios Inc.; Janssen Research & Development LLC retains operational responsibility for the ASCEND-HF study. Singulex, Inc. performed all plasma IL-6 assays, and was blinded from the trial database or analyses. Previously, Ortho-Clinical Diagnostic performed all NT-proBNP assays. Statistical analyses, and manuscript preparation were conducted independent of the sponsors, and the authors have access to all the data in its entirety and approved the final manuscript.

See page 675 for disclosure information.

1071-9164/\$ - see front matter

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<https://doi.org/10.1016/j.cardfail.2021.01.006>

and readmission in hospitalized patients with acute HF, using randomized controlled data obtained from the ASCEND-HF trial.

Methods

Study Population

Details of ASCEND-HF have been published previously.¹⁹ Concisely, the ASCEND-HF trial was a multicenter, randomized, double-blind, placebo-controlled trial that demonstrated the effects of nesiritide vs placebo added to standard treatment in 7141 patients diagnosed with acute HF requiring hospitalization. Our biomarker substudy recruited patients enrolled in the ASCEND-HF study who consented to collection of plasma samples at baseline, 48–72 hours, and at 30 days after randomization, as previously described.^{20–26} Patients on inotropes, vasopressors, and mechanical circulatory support were excluded. All laboratory analyses were performed in a core laboratory. Plasma IL-6 levels were measured by the Erenna IL-6 Immunoassay Kit (Singulex, Inc., Alameda, CA).²⁷

Clinical End Points

In this IL-6 biomarker substudy, the following adjudicated endpoints were analyzed: all-cause mortality at 30 days, death or rehospitalization at 30 days, and all-cause mortality at 180 days.¹⁹

Statistical Analyses

Baseline characteristics are presented as a percentage for categorical values, mean $\pm$ standard deviation for normally distributed continuous variables, and median (interquartile range [IQR]) for non-normally distributed continuous variables. We used Cochran–Armitage and Jonckheere–Terpstra

tests of trend to compare baseline characteristics across increasing tertiles of IL-6 at baseline for categorical and continuous variables, respectively. Statistical significance was determined by 2-sided *P* values of .05 or less. Plasma IL-6 and amino terminal pro-B-type natriuretic peptide (NT-proBNP) levels had a skewed distribution and were accordingly log-transformed. The Kaplan–Meier method and log-rank test were used to estimate survival curves for each IL-6 tertile. The association between IL-6 and outcomes was performed using Cox proportional hazards analysis. The covariates used for multivariable analyses were obtained from the ASCEND-HF risk model and were outcome-specific (Supplementary Table 1).²⁰ Levels of IL-6 at baseline, 48–72 hours, and 30 days were compared between the patients receiving nesiritide and placebo using the Wilcoxon rank-sum test. For all outcome analyses, an interaction test was performed between IL-6 and nesiritide treatment with the ASCEND-HF risk model.

Results

Patient Characteristics and IL-6 Levels

Baseline characteristics of this ASCEND-HF biomarker substudy population (*n* = 883) stratified by baseline IL-6 tertiles are illustrated in Table 1. In our study population, the median baseline IL-6 was 14.1 pg/mL (IQR 8.1–26.4 pg/mL), decreasing to 12.3 pg/mL (IQR 7.6–21.1 pg/mL) at 48–72 hours, and 7.6 pg/mL (IQR 4.5–14.2 pg/mL) at 30 days. Age, higher blood urea nitrogen, higher creatinine, higher NT-proBNP, and ischemic etiology were associated with higher IL-6 levels at baseline. In contrast, the use of beta-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists were associated with lower IL-6 levels. There was no significant difference in the median baseline IL-6 levels between ischemic and

Table 1. Baseline Characteristics

Characteristics	Baseline IL-6 (pg/mL)				<i>P</i> Value
	Total (<i>N</i> = 883)	<9.9 (<i>n</i> = 292)	9.9–20.4 (<i>n</i> = 298)	≥20.4 (<i>n</i> = 293)	
Age (years)	65.6 $\pm$ 15.2	62.7 $\pm$ 15.5	66.6 $\pm$ 14.8	67.4 $\pm$ 14.8	<.001
Sex (female %)	31.5	34.6	29.5	30.4	<.001
Race (White, %)	68.1	59.6	68.5	76.1	<.001
Systolic BP (mm Hg)	127.1 $\pm$ 20.0	130.2 $\pm$ 21.4	124.7 $\pm$ 19.0	126.5 $\pm$ 19.2	.054
Heart rate (bpm)	80.4 $\pm$ 16.5	79.7 $\pm$ 15.6	79.9 $\pm$ 16.2	81.8 $\pm$ 17.5	.208
Hypertension (%)	78.0	85.3	77.9	71.0	<.001
BUN (mg/dL)	28.8 $\pm$ 17.2	24.6 $\pm$ 13.3	29.6 $\pm$ 18.1	32.3 $\pm$ 18.8	<.001
Creatinine (mg/dL)	1.5 $\pm$ 0.6	1.4 $\pm$ 0.5	1.5 $\pm$ 0.6	1.5 $\pm$ 0.6	.002
Sodium (mmol/L)	138.5 $\pm$ 4.0	138.7 $\pm$ 3.9	138.6 $\pm$ 3.9	138.3 $\pm$ 4.1	.051
NT-proBNP (pg/mL)	5972 (2985–11,618)	4262 (2290–9128)	5524 (3130–11,622)	8297 (3918–14,687)	<.001
LVEF (%)	26 (20–40)	26 (20–37)	25 (20–40)	30 (20–44)	.105
Ischemic etiology(%)	60.0	59.6	57.7	62.8	<.001
Beta-blockers (%)	74.7	76.4	75.5	72.4	<.001
ACEi or ARB (%)	64.2	66.4	64.4	61.8	<.001
MRA (%)	24.6	28.8	23.2	21.8	<.001

Values are mean $\pm$ SD or median (interquartile range), unless otherwise indicated. All *P* values are from test of trend (Jonckheere–Terpstra test for continuous and Cochran–Hermitage test for categorical variables).

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; BUN, blood urea nitrogen; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, amino terminal pro-B-type natriuretic peptide.

Fig. 1. Kaplan–Meier analysis for 180-day survival, stratified by tertiles of (A) baseline (tertile ranges: tertile 1 = <9.9 pg/mL; tertile 2 = 9.9 to 20.4 pg/mL; tertile 3 = >20.4), (B) 48–72 h (tertile ranges: tertile 1 = <9 pg/mL; tertile 2 = 9 to 17.4 pg/mL; tertile 3 = >17.4), and (C) 30-day (tertile ranges: tertile 1 = <5.5 pg/mL; tertile 2 = 5.5 to 11.5 pg/mL; tertile 3 = >11.5) plasma IL-6 levels.

nonischemic etiologies (13.0 pg/mL [IQR 7.7–26.3 pg/mL] vs 14.8 pg/mL [IQR 8.4–26.5 pg/mL], $P = .14$). Although it did not reach statistical significance, it is interesting that patients in the highest tertile for IL-6 had also had the highest left ventricular ejection fraction at baseline. At 30 days, there were 26 deaths (2.9%) and 103 (11.7%) rehospitalizations for HF. There were also 101 deaths (11.4%) at 180 days.

IL-6 Levels at Baseline and Adverse Clinical Outcomes

Fig. 1 shows the association between IL-6 levels at baseline and 180-day mortality. Participants with baseline IL-6 levels in the third tertile (≥ 20.4 pg/mL) had a 1.74-fold higher risk in mortality at 180 days than the first tertile (hazard ratio [HR] per log: 1.74; 95% confidence interval [CI] 1.09–2.78; $P = .021$, Table 2). There was also higher 30-day mortality among patients with baseline IL-6 levels in the third tertile in comparison with the first tertile (HR 3.23 per log; 95% CI 1.18–8.86, $P = .022$). The unadjusted IL-6 at baseline was significantly associated 180-day mortality

(HR per log 1.26, 95% CI 1.04–1.53, $P = .018$). After multivariable adjustment with the ASCEND-HF risk model (with and without baseline NT-proBNP), the IL-6 level at baseline was not independently associated with 30-day mortality, 180-day mortality, or 30-day death or rehospitalization (Table 2) rates.

IL-6 Levels at 48–72 Hours and 30 Days and Adverse Clinical Outcomes

Among the 883 patients in this ASCEND-HF biomarker substudy, there were 702 and 641 patients who had samples at 48–72 hours and 30 days, respectively. IL-6 at 48–72 hours was independently associated with 30-day mortality when adjusted with the ASCEND-HF risk model (HR per log 8.52, 95% CI 1.19–61.2, $P = .03$, Table 3) and with the ASCEND-HF risk model plus baseline NT-proBNP (HR per log 8.2, 95% CI 1.2–57.5, $P = .03$). IL-6 at 48–72 hours and at 30 days were found to be associated with 180-day mortality (HR per log 2.78, 95% CI 1.53–5.05, $P = .001$ and HR per log 3.28, 95% CI

Table 2. Baseline IL-6 Levels by tertiles and Adverse Clinical Outcomes with the ASCEND-HF Risk Model and NT-proBNP

Outcomes		Baseline IL-6 Levels (Range)			
		Tertile 1 (<9.9 pg/mL)	Tertile 2 (9.9 – 20.4 pg/mL)	<i>P</i> Values	Tertile 3 (≥ 20.4 pg/mL)
Death at 30 days					
Unadjusted HR	Reference		0.97 (0.28-3.35)	.96	3.23 (1.18-8.86)
Adjusted HR (1)	Reference		1.18 (0.28-5.01)	.83	3.31 (0.93-11.82)
Adjusted HR (2)	Reference		1.24 (0.30-5.18)	.77	3.12 (0.89-10.90)
Death or rehospitalization at 30 days					
Unadjusted HR	Reference		1.05 (0.63-1.75)	.84	1.51 (0.94-2.41)
Adjusted HR (1)	Reference		0.99 (0.58-1.69)	.98	1.32 (0.80-2.17)
Adjusted HR (2)	Reference		0.91 (0.53-1.56)	.73	1.07 (0.64-1.80)
Death at 180 days					
Unadjusted HR	Reference		0.94 (0.55-1.59)	.81	1.74 (1.09-2.78)
Adjusted HR (1)	Reference		0.71 (0.39-1.28)	.25	1.34 (0.77-2.32)
Adjusted HR (2)	Reference		0.69 (0.37-1.27)	.23	1.06 (0.61-1.87)

ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; CI, confidence interval; HF, heart failure; HR, hazard ratio.

Both IL-6 and NT-proBNP (amino terminal pro-B-type natriuretic peptide) were log transformed, increments per log increase. Adjusted model 1 = ASCEND-HF trial risk model according to endpoints; adjusted model 2 = model 1 with NT-proBNP.

Table 3. IL-6 Levels at 48–72 Hours and 30 Days by Tertiles and Adverse Clinical Outcomes with the ASCEND-HF Risk Model and NT-proBNP

Outcomes	IL-6 levels at 48-72 hours				
	Tertile 1 (<9.0 pg/mL)	Tertile 2 (9.0–17.4 pg/mL)	P Values	Tertile 3 (≥17.4 pg/mL)	P Values
Death at 30 days					
Unadjusted HR	Reference	1.98 (0.36–10.8)	.43	6.65 (1.5–29.46)	.01
Adjusted HR (1)	Reference	3.28 (0.38–28.6)	.28	8.52 (1.19–61.16)	.03
Adjusted HR (2)	Reference	3.10 (0.36–26.6)	.30	8.20 (1.17–57.54)	.03
Death or rehospitalization at 30 days					
Unadjusted HR	Reference	0.74 (0.43–1.28)	.29	1.18 (0.72–1.92)	.51
Adjusted HR (1)	Reference	0.67 (0.38–1.18)	.16	0.94 (0.56–1.55)	.80
Adjusted HR (2)	Reference	0.61 (0.34–1.09)	.09	0.81 (0.48–1.38)	.44
Death at 180 days					
Unadjusted HR	Reference	1.38 (0.71–2.68)	.34	2.78 (1.53–5.05)	.001
Adjusted HR (1)	Reference	1.26 (0.62–2.57)	.53	1.57 (0.81–3.03)	.18
Adjusted HR (2)	Reference	1.14 (0.56–2.31)	.71	1.36 (0.69–2.67)	.37
IL-6 levels at 30 days					
Outcomes	Tertile 1 (<5.5 pg/mL)	Tertile 2 (5.5–11.5 pg/mL)	P Values	Tertile 3 (≥11.5 pg/mL)	P Values
Death at 180 days					
Unadjusted HR	Reference	2.1 (0.91–4.86)	.08	3.28 (1.48–7.26)	.003
Adjusted HR (1)	Reference	1.41 (0.52–3.79)	.50	2.11 (0.77–5.76)	.15
Adjusted HR (2)	Reference	1.34 (0.50–3.58)	.56	2.00 (0.73–5.46)	.18

Abbreviations as in Table 2.

Both IL-6 and NT-proBNP were log transformed, increments per log increase. Adjusted model 1 = ASCEND-HF trial risk model according to endpoints; adjusted model 2 = model 1 with NT-proBNP.

1.48–7.26, $P = .003$, respectively). These associations, however, did not persist when adjusting for the ASCEND-HF risk model (with and without NT-proBNP).

Associations between changes in IL-6 levels at 48–72 hours and 30 days from baseline and adverse clinical outcomes were also evaluated. The median absolute changes in IL-6 from baseline were -1.2 pg/mL (IQR -8.3 to 3.6 pg/mL) at 48–72 h, and -4.4 pg/mL (IQR -14.1 to 0.4 pg/

mL) at 30 days. At 30 days, 25.9% of patients experienced an increase in IL-6 levels compared with baseline. There was significantly greater risk of death at 180 days in patients who experienced an increase in IL-6 from baseline to 30 days vs those who had no change or a decrease during this period (HR per log 2.16, 95% CI 1.23–3.78, $P = .007$, Fig. 2). However, this difference did not persist after adjustment with the ASCEND-HF risk model (with and without

Fig. 2. Change in plasma IL-6 from baseline to 30 days and all-cause mortality.

Fig. 3. Impact of nesiritide therapy on IL-6 levels at baseline, 48–72 hours, and 30 days.

NT-proBNP). There was no significant association between absolute change in IL-6 from baseline to 30 days and 180-day mortality.

IL-6 and Nesiritide

In this ASCEND-HF biomarker substudy cohort, there were 444 patients in the nesiritide group and 439 patients in placebo group. We assessed the treatment effects of either nesiritide or placebo on IL-6 levels at baseline, 48–72 hours, and 30 days as illustrated in Fig. 3. At all time points, there was no significant difference in IL-6 levels between the patients receiving nesiritide vs placebo. There was no interaction between IL-6 levels and nesiritide treatment when adjusted with ASCEND-HF risk model (Supplementary Table 2, all $P > .05$).

Discussion

There are several major findings in this study. First, the median IL-6 levels decreased during the first 30 days after randomization in a contemporary cohort of hospitalized acute HF patients. Second, IL-6 levels correlated with NT-proBNP in this population. Third, use of guideline-directed medical therapy (beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and/or mineralocorticoid receptor antagonists) was associated with lower IL-6 in comparison with patients not receiving these treatments. Fourth, IL-6 levels in acute HF at baseline and after 30 days correlated, but were not independently associated with 180-day mortality. Fifth, IL-6 at 48–72 hours after hospitalization was found to be independently associated with 30-day, but not 180-day mortality after adjusting for the ASCEND-HF risk model with NT-proBNP. Sixth,

an increase in IL-6 from baseline to 30 days correlated but was not independently associated with 180-day mortality. Seventh, nesiritide did not impact IL-6 levels in acute HF when compared with placebo.

Recently, a substudy of the BIOSTAT-CHF trial showed that IL-6 was a predictor of all-cause mortality in a cohort of more than 2300 at-home and hospitalized patients with worsening HF symptoms.¹⁴ There are several important differences between our ASCEND-HF IL-6 substudy and the BIOSTAT-CHF IL-6 substudy that make a direct comparison between the 2 cohorts difficult. Approximately one-third of the BIOSTAT-CHF patients were not hospitalized. Furthermore, blood samples in BIOSTAT-CHF were not consistently obtained on day 1 of the study period, owing to the observational nature of the study. Last, the enrollment criteria for BIOSTAT-CHF excluded patients on more than 50% of target dose beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Interestingly, IL-6 measured 48–72 hours after baseline in our study cohort did independently predict mortality at 30 days and 180 days. When NT-proBNP was added as a covariate, IL-6 at this time point was no longer independently associated with 180-day mortality. This point raises the possibility that IL-6 several days after treatment initiation in acute HF may identify a high-risk group in which inflammation may be an important component of their pathophysiology.

It is important to note that a causal relation between circulating interleukin levels and HF has not been confirmed, although a causal association between circulating interleukins and atherosclerosis leading to cardiovascular and cerebrovascular diseases has been previously established.²⁸ This finding is likely related to the complexity of the HF

syndrome that represents many different physiopathologic processes at different stages of progression not restricted to a single inflammatory pathway. Indeed, IL-6 levels have been previously evaluated in the acute HF setting, along with high-sensitivity C-reactive protein and IL-1, showing no significant association with either renal impairment, persistent congestion, or an adverse outcome.²⁹ Thus, these cytokines, which are considered reliable markers of systemic inflammation, may not reflect specific inflammatory pathways in vascular and myocardial diseases. The observation that a trend toward higher IL-6 levels in patients with higher left ventricular ejection fraction is consistent with an inflammatory phenotype in some patients with HF with preserved ejection fraction.³⁰

Our study contradicts a prior report that implicated nesiritide as a modulator of IL-6 in acute HF.¹⁸ In that prior study involving 66 hospitalized patients with acute HF randomized to nesiritide vs nitroglycerin infusion, those who received nesiritide but not nitroglycerin experienced a significant decrease in IL-6 from baseline to 48 hours. In our larger substudy from the double-blind randomized controlled trial ASCEND-HF, we found no significant difference in serial IL-6 measurements between patients who received nesiritide vs placebo. Formal testing also did not show any interaction between nesiritide and IL-6. Our study indicates that nesiritide does not modulate plasma IL-6 in acute HF.

Conclusions

Although elevated IL-6 levels were associated with higher all-cause mortality in acute HF, no independent association with this outcome was identified at baseline and 30-day measurements. Contrary to prior reports, we did not observe any impact of nesiritide over placebo on serial IL-6 levels.

Disclosures

A. Perez is a consultant and advisory board member for Abiomed. J. Grodin is a consultant and advisory board member for Eidos Therapeutics, Alnylam, and Pfizer. T. Chaikijurajai and Y. Wu have no disclosures. A. F. Hernandez has received research grants from Johnson & Johnson. J. Butler is a consultant and advisory board member for Abbott, Amgen, Applied Therapeutics, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Relypsa, and Vifor. M. Metra is a consultant and advisory board for Abbott Vascular, Amgen, Astra-Zeneca, Bayer, Edwards Therapeutics, Vifor Pharma, and Servier. G. M. Felker has received research grants from Johnson & Johnson, Roche Diagnostics, Critical Diagnostics, and BG Medicine. A. A. Voors is a consultant and advisory board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia, Novartis, NovoNordisk, Roche Diagnostics, and Vifor.

J. J. McMurray has received payments to my employer, Glasgow University, for my work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, Theracos; and personal lecture fees from Abbott, Hikma, Sun Pharmaceuticals, and Servier. P. W. Armstrong has received research grants from Johnson & Johnson and Ortho Biotech. C. M. O'Connor has received research grants from Johnson & Johnson. R. C. Starling has received other research support from Johnson & Johnson; and is a consultant and advisory board for Johnson & Johnson. W. Tang is a consultant and advisory board member for Sequana Medical Inc, Owkin Inc, and Relypsa Inc.

Supplementary materials

Supplementary material associated with this article can be found in the online version at [10.1016/j.cardfail.2021.01.006](https://doi.org/10.1016/j.cardfail.2021.01.006).

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