Heart failure or heart success?

Teramoto, Kanako; Tromp, Jasper; Lam, Carolyn S. P.

Published in:
Cardiovascular Research

DOI:
10.1093/cvr/cvab022

Publication date:
2021

ESC European Society of Cardiology

Cardiovascular Research (2021) **117**, e29–e34
doi:10.1093/cvr/cvab022

CLINICAL COMMENTARIES

CARDIOVASCULAR RESEARCH Onlife

Heart failure or heart success?

Kanako Teramoto [1], Jasper Tromp[2,3,4], and Carolyn S. P. Lam[2,3,4,5]*

[1]Department of Cardiology, St. Marianna University School of Medicine, Kanagawa, Japan; [2]National Heart Centre Singapore, Singapore; [3]Duke-National University of Singapore, Singapore; [4]Department of Cardiology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands; and [5]The George Institute for Global Health, Sydney, Australia

Keywords HFrEF • Cardiac myosin • Ferric carboxymaltose • Sotagliflozin

For decades, anti-failure therapy for heart failure with reduced ejection fraction (HFrEF) was synonymous with the triple foundational therapy of angiotensin-converting enzyme (ACE) inhibitors, mineralocorticoid-receptor antagonists (MRA), and β-blockers. In the last decade, a paradigm shift occurred with the success of respectively named trials (PARADIGM-HF[1] and SHIFT[2]) adding sacubitril/valsartan and ivabradine to the HFrEF armamentarium. In the last year alone, further successful trials added the sodium-glucose cotransporter-2 (SGLT2) inhibitors (namely dapagliflozin and empagliflozin) as the fourth foundational pillar in HFrEF treatment,[3,4] and the soluble guanylate cyclase stimulator vericiguat as an option for patients with worsening HFrEF. Success continued with the recent presentation of three further trials: the Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF), A Randomised, Double-blind Placebo-Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure (AFFIRM-AHF), and Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trials.[5–7] This commentary aims to place these latest three trials in the context of recent trials (*Table 1*).

GALACTIC-HF was a large randomized controlled event-driven trial of omecamtiv mecarbil—a first-in-class cardiac myosin activator which improves cardiac contractility—compared to placebo, added on top of standard therapy in HFrEF. Omecamtiv mecarbil reduced the primary composite endpoint of CV death or HF event (either HF hospitalization or urgent outpatient visit) by 8% [hazard ratio (HR) 0.92; 95% confidence interval (CI) 0.86–0.99; $P = 0.03$] with no impact on blood pressure and without a meaningful increase in safety events (a 4 ng/L increase in troponin I in the treatment arm did not translate to more major ischaemic or ventricular arrhythmic events compared to the placebo arm). Unique about the trial population was the inclusion of both in- and outpatients, with lower left ventricular (LV) EF and blood pressure cut-offs than other recent HF trials (*Table 1*). Thus, GALACTIC-HF provides the first outcome evidence of a safe reduction in HF events with a novel inotrope. Yet, where omecamtiv mecarbil fits in the selection and sequencing of HFrEF therapies remains unclear. The effect on the primary endpoint was modest, both in terms of relative and absolute risk reduction, and there was no mortality benefit in this well-powered trial. Coupled with the need for plasma level-guided dose titration, omecamtiv mecarbil is unlikely to be included as part of the standard treatment regimen for the majority of patients with HFrEF. In terms of subgroups that may benefit more than others, the relative risk reduction was stronger in patients with LVEF ≤ 28% than in those with higher LVEF (interaction $P = 0.003$). Given the mode of action of the drug, this is not surprising—but would also position omecamtiv mecarbil as a possible add-on therapy in patients with severe systolic dysfunction, in whom hypotension is often a complicating issue for conventional treatment.

AFFIRM-AHF was a multicentre, randomized, placebo-controlled trial, testing whether intravenous iron treatment with ferric carboxymaltose reduced post-discharge morbidity and mortality in patients hospitalized with acute HFrEF (LVEF <50%) who had iron deficiency (defined by serum ferritin < 100 ng/mL or a transferrin saturation < 20% if serum ferritin was between 100 and 299 ng/mL). In contrast to the event-driven design of other recent HF trials (*Table 1*), the primary outcome of AFFIRM-AHF was a composite of total HF hospitalizations and CV death up to 52 weeks post-randomization, and a modified intention-to-treat approach was used, including patients who received at least one dose of study treatment and for whom at least one follow-up data point was known. The trial narrowly missed statistical significance, showing a lower rate of the primary outcome with intravenous iron compared to placebo [rate ratio (RR) 0.79, 95% CI 0.62–1.01; $P = 0.059$], with no difference in CV death.

The conduct of AFFIRM-AHF was complicated by the COVID-19 pandemic, with results for the primary outcome becoming statistically significant after censoring patients in each country on the date when the first patient with COVID-19 was reported in the respective country (RR 0.75, 95% CI 0.59–0.96; $P = 0.024$). While the COVID-19 sensitivity analysis was meaningful in view of reported associations of the pandemic with reduced HF hospitalization rates[8] that may particularly impact recurrent HF events in the trial, how such analyses will be viewed in guidelines remains unknown. Of note, exploratory analyses using the 'traditional' composite of first HF hospitalization or CV death yielded statistically significant benefit with IV iron (RR 0.80, 95% CI 0.66–0.98). The totality of the evidence, including prior studies of ferric carboxymaltose for iron deficiency in both HF and chronic kidney disease, confirm that

*Corresponding author. Tel: (65) 6704 8000; E-mail: Carolyn.lam@duke-nus.edu.sg

Table 1 Recent major heart failure trials in context

	GALACTIC-HF	AFFIRM-AHF	SOLOIST-WHF	VICTORIA	EMPEROR-Reduced	DAPA-HF	PARADIGM-HF
Total randomized patients	8256	1132	1222	5050	3730	4744	8442
Treatment arm medication	Omecamtiv mecarbil	Intravenous ferric carboxymaltose	Sotagliflozin	Vericiguat	Empagliflozin	Dapagliflozin	Sacubitril/Valsartan[b]
Inclusion criteria							
Enrolment setting	Inpatient (~25%)/ outpatient	Inpatient	Inpatient	Inpatient/outpatient	Outpatient	Outpatient	Outpatient
LVEF (%)	≤35	<50	Any	<45	≤40	≤40	≤40[c]
BNP (pg/mL)	≥125 at screening (or ≥375 for Afib/AFL)	≥400 at max 72 h after admission (≥ 600 for Afib)	≥150 at randomization (≥ 450 for Afib)	≥300, within 30 days prior to randomization (or ≥ 500 for Afib)	Not defined	Not defined	≥150 at screening (or ≥100 within the last 12 months HFH)
NT-proBNP (pg/mL)	≥400 at screening[a] (or ≥ 1200 for Afib/AFL) Those on ARNi must be using NT-proBNP	≥1600 at max 72 h after admission (≥ 2400 for Afib)	≥600 at randomization (≥ 1800 for Afib)	≥1000, 30 days prior to randomization (or ≥ 1600 for Afib)	[LVEF ≤ 30%; ≥ 600 (1200 for Afib/ALF)] [LVEF > 30% & ≤ 35%; ≥ 1000 (2000 for Afib/ALF)] [LVEF > 36% & ≤ 40%; ≥ 2500 (5000 for Afib/ALF)] [LVEF ≤ 40% & HFH within 12 months prior; ≥ 600 (1200 for Afib/ALF)]	≥ 600 at screening (or ≥ 400 within the last 12 months HFH) (≥ 900 for Afib/AFL)	≥600 at screening (or ≥ 400 within the last 12 months HFH)
Exclusion criteria							
eGFR (mL/min/1.73 m^2)	<20	Renal dialysis (performed or planned)	<30	≤15	<20	<30	<30
SBP (mmHg)	<85	–	<100	<100	<100	<95	<100
Potassium (mmol/L)	–	–	>5.5	–	–	–	>5.2
Baseline characteristics							
Age (years), mean (SD) or median (Q1–Q3)	64.5 (11.3)	71.2 (10.8)	69 (63–76)	67.3 (12.2)	66.9 (11.0)	66.4 (11)	63.8 (11.4)
Female sex, *n* (%)	1756 (21.3)	244 (44.0)	198 (32.6)	1208 (23.9)	893 (23.9)	1109 (23.4)	1832 (22.0)
Index event, *n* (%)							
Inpatient for HF	2084 (25.2)	558 (100)	608 (100)	571 (11.3)	–	–	–
HF hospitalization within 3 months	2992 (36.2)	-	-	3378 (66.9)	–	368 (7.8)	1611 (19.1)
IV diuretic for HF within 3 months (no hospitalization)	–	-	-	801 (15.9)	–	–	–
HF hospitalization 3–6 months	1523 (18.4)	-	-	871 (17.2)	–	410 (8.6)	1009 (12.0)

Continued

Table I *Continued*

	GALACTIC-HF	AFFIRM-AHF	SOLOIST-WHF	VICTORIA	EMPEROR-Reduced	DAPA-HF	PARADIGM-HF
HF hospitalization >6 months	1636 (19.8)	-	-	0	–	1473 (31.0)	2632 (31.2)
LVEF (%), mean (SD) or median (Q1–Q3)	26.6 (6.3)	32.6 (9.6)	35 (28–47)	28.9 (8.3)	27.5 (6.1)	31.1 (6.8)	29.5 (6.2)
NYHA class, *n* (%)							
I	0	14 (3%)	–	2 (0.0)	0	0	389 (4.7)
II	4391 (53.2)	255 (46)	–	2975 (59.0)	2800 (75.1)	3203 (67.5)	5919 (70.9)
III	3616 (43.8)	272 (49)	–	2003 (39.7)	910 (24.4)	1498 (31.6)	2018 (24.1)
IV	248 (3.0)	16 (3)	–	66 (1.3)	20 (0.5)	43 (0.9)	60 (0.7)
KCCQ total symptom score, median (Q1–Q3)	68.8 (49.0–87.5)	–	35 (28-44) [KCCQ-12 score]	–	–	77.1 (58.3–91.7)	83.3 (67.7–95.8)
SBP (mmHg), mean (SD) or median (Q1–Q3)	117 (15)	119.8 (15.2)	122 (111–135)	121 (16)	122 (15)	122 (16)	121 (15)
NT-proBNP (pg/mL), median (Q1–Q3)	1971 (962–4033)	4743 (2781–8128)	1816.8 (855–3659)	2816 (1556–5314)	P: 1926 (1153–3525) E: 1887 (1077–3429)	1437 (857–2649)	1608 (886–3221)
eGFR (mL/min/1.73 m^2), mean (SD) or median (Q1–Q3)	60.3 (21.8)	eGFR <60 292 (52%)	49.2 (39.5–61.2)	61.5 (27.2)	62.0 (21.6)	65.8 (19.4)	70 (20)
Medications and cardiac devices, *n* (%)							
ACEi, ARB, or ARNi	7161 (86.7)	ACEi 293 (53) ARB 97 (17)	Any RAAS inhibitor (MRA included) 553 (91.0)	3700 (73.4)	3327 (89.2)	4476 (94.4)	8339 (100)
ARNi	1594 (19.3)	35 (6)	93 (15.3)	731 (14.5)	727 (19.5)	508 (10.7)	–
BB	7763 (94.0)	453 (81)	564 (92.8)	4691 (93.1)	3533 (94.7)	4558 (96.1)	7811 (93.6)
MRA	6358 (77.0)	376 (67)	403 (66.3)	3545 (70.3)	2661 (71.3)	3370 (71.0)	4671 (55.3)
(ACEi, ARB, or ARNi)+MRA+BB	5367 (65.0)	–	–	3009 (59.7)	–	3097 (65.3)	(≤55.3)
ICD	2614 (31.7)	67 (12)	–	1399 (27.8)	1171 (31.4)	1242 (26.2)	2539 (14.9)
CRT	1156 (14.0)	33 (6)	–	739 (14.7)	442 (11.8)	354 (7.5)	574 (6.8)
Trial outcomes							
Median follow-up (months)	21.8	–	9.0	10.8	16	18.2	27
Primary endpoint (defined by trials)	CV death or HF event (HFH or urgent outpatient visit)	Total HFH and CV death	Total number of CV death, HFH, urgent visits for HF (first and subsequent)	CV death or HFH	CV death or HFH	CV death or HF worsening (HFH or urgent visit)	CV death or HFH
HR (95% CI)	0.92 (0.86–0.99)	0.79[d] (0.62–1.01)	0.67 (0.52–0.85)	0.90 (0.82–0.98)	0.75 (0.65–0.86)	0.74 (0.65–0.85)	0.80 (0.73–0.87)
Control arm annualized event rate (per 100 pt-yrs)	26.3	72.5	76.3	37.8	21.0	15.6	13.2
ARR	2.1	15.4	25.3	4.2	5.2	4.0	2.7

Continued

Table I *Continued*

	GALACTIC-HF	AFFIRM-AHF	SOLOIST-WHF	VICTORIA	EMPEROR-Reduced	DAPA-HF	PARADIGM-HF
CV death or HF hospitalization (first)							
HR (95% CI)	–	0.80 (0.66–0.98)	0.71 (0.56–0.89)	0.90 (0.82–0.98)	0.75 (0.65–0.86)	0.75 (0.65–0.85)	0.80 (0.73–0.87)
Control arm annualized event rate (per 100 pt-yrs)	–	47.1	–	37.8	21.0	15.3	13.2
ARR	–	9.7	–	4.2	5.2	3.9	2.7
CV death							
Total CV death	P; 798 (19.4)	P; 78 (14.2)	P; 58 (9.4)	P; 441 (17.5)	P; 202 (10.8)	P; 273 (11.5)	Enalapril; 693 (16.5)
Number, cases (%)	OM; 808 (19.6)	FC; 77 (13.8)	S; 51 (8.4)	V; 414 (16.4)	E; 187 (10.0)	D; 227 (9.6)	SV; 558 (13.3)
HR (95% CI)	NS	NS	NS	NS	NS	0.82 (0.69–0.98)	0.80 (0.71–0.89)
Control arm annualized event rate (per 100 pt-yrs)	10.8	16.1	12.5	13.9	8.1	7.9	7.5
ARR	–	0.2	1.9	1.0	0.5	1.4	1.5
Adverse event[e]							
Overall adverse event to discontinuation, %	P; 9.3 OM; 9.0	P; 17.4 FC; 17.5	P; 3.8 S; 4.8	P; 6.3 V; 7.0	P; 8.9 E; 8.5	P; 4.9 D; 4.7	Enalapril; 12.3 SV; 10.7
Hypotension, %	P; 6.6 OM; 7.5	–	P; 4.6 S; 6.0	P; 14.1 V; 15.4	P; 8.7 E; 9.4	P; 0.5 D; 0.3	Enalapril; 12.0 SV; 17.6
Renal failure, %	P; 5.5 OM; 5.6	–	P; 4.4 S; 4.1	P; 3.5 V; 3.7	–	P; 6.7 D; 6.0	Enalapril; 3.4 SV; 2.6
Hyperkalaemia, %	P; 5.6 OM; 5.3	–	P; 5.1 S; 4.3	P; 5.6 V; 4.4	–	P; 0.2 D; 0.1	Enalapril; 14.0 SV; 11.6
Cardiac disorders/failure, %	P; 6.4 OM; 5.4	P; 44.3 FC; 40.1	P; 26.4 S; 18.5	P; 10.7 V; 8.1	–	P; 26.8 D; 22.0	Enalapril; 19.7 SV; 17.4
Hypoglycaemic, %	–	–	P; 2.8 S; 4.3	–	P; 1.5 E; 1.4	P; 0.2 D; 0.2	–
Diarrhoea, %	–	–	P; 3.4 S; 6.1	P; 4.9 V; 5.2	–	P; 0.2 D; 0.2	Enalapril; 4.5 SV; 4.6

[a]Those on who were on ARNi prior to enrolment must use NT-proBNP for entry criteria.
[b]The comparator drug for PARADIGM-HF was enalapril.
[c]Later reduced to 35%.
[d]Presented as rate ratio.
[e]The definitions of adverse events vary by trials.
Demographics and background characteristics for AFFIRM-AHF and SOLOIST-WHF (shaded grey) are for those in the treatment arm only (data were not available for the overall cohort).
ACEi, angiotensin-converting enzyme inhibitor; Afib; atrial fibrillation; AFL, atrial flutter; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; ARR, absolute risk reduction; BB, beta-blocker; CI, confidence interval; CRT, cardiac resynchronization therapy; CV, cardiovascular; D, dapagliflozin; E, empagliflozin; eGFR, estimated glomerular filtration rate; FC, ferric carboxymaltose; HF, heart failure; HFH, heart failure hospitalization; ICD, implantable cardioverter defibrillator; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NS; not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OM, omecamtiv mecarbil; P, placebo group; pt-yrs, patient-years; S, sotagliflozin; SBP, systolic blood pressure; SD, standard deviation; SOC, standard of care; SV, sacubitril valsartan; V, vericiguat; –, not available.

iron deficiency is an important treatable comorbidity in HFrEF. The apparent greater benefit in patients with ischaemic, compared to non-ischaemic, HFrEF (*P* for interaction 0.015) requires further interrogation.

Another trial impacted by COVID-19 was SOLOIST-WHF, a randomized controlled trial, intended as event-driven, to assess the effect of sotagliflozin (a dual SGLT1 and SLGT2 inhibitor) in patients with type 2 diabetes hospitalized for acute decompensated HF, regardless of LVEF. Loss of industry funding amid the pandemic led to the trial stopping after randomization of only 1222 (instead of the originally targeted ~4000) patients, with investigators deciding before unblinding to change the primary endpoint to total CV deaths and HF events, and to use investigator-reported events without adjudication. Results showed an impressive reduction with sotagliflozin in the new primary endpoint of total CV deaths, HF hospitalizations and urgent visits for HF (HR 0.67, 95% CI 0.52–0.85), as well as the original primary endpoint of first HF hospitalization or CV death (HR 0.71, 95% CI 0.56–0.89). In terms of safety, higher rates of diarrhoea and severe hypoglycaemia were observed, in contrast to prior trials of SGLT2 inhibitors, presumably due to the additional increase in glucose elimination via SGLT1 inhibition in the gastrointestinal tract by sotagliflozin. No differences in volume depletion or kidney failure were observed. Perhaps most tantalizing are the implications of SOLOIST-WHF for the safe initiation of SGLT inhibitors in hospitalized patients, as well as possible benefit in patients with HF and preserved LVEF.

An assessment of these trials in the context of other recent successes (*Table 1*) reveals important take-home messages: trial outcomes must be viewed in relation to the baseline risk of the study population, where those randomized in-hospital or close in proximity to their HF hospitalization are at higher risk of adverse outcomes (compared to more 'stable' outpatients), and thus accrue a greater absolute risk reduction for any given relative risk reduction. Thus, patients in AFFIRM-AHF and SOLOIST-WHF had impressive absolute risk reductions, translating to small numbers needed to treat to realize the therapeutic effect. In this regard, the subgroup of in-hospital patients in GALACTIC-HF will be of interest when results become available. CV mortality reduction was demonstrated with statistical significance only in DAPA-HF and PARADIGM-HF; but AFFIRM-AHF, SOLOIST-WHF, and EMPEROR-Reduced had fewer numbers of CV deaths in comparison and may therefore have been underpowered for this outcome. The majority of patients in recent trials were well-treated on baseline triple foundational therapy, thus showing that the newer therapies offered incremental benefit to the existing standard of care; however, because the newer trials were largely conducted simultaneously, rather than sequentially, results cannot guide the sequencing of therapeutic choices. Clinicians are left to assess the relative benefits of new therapies and select the best combination for their patients, reasoning that since each of the new drugs modulates biologically different pathways,[9] the combined benefits are potentially additive. The concern remains the safety, tolerability, and affordability of different combinations, which future real-world observational studies will hopefully address.

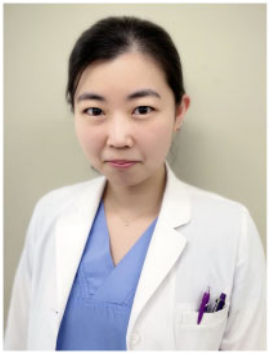
The field of HF has witnessed astounding success in recent times. Such successes are needed to address the significant residual risk in patients with HFrEF already receiving existing standard of care. While celebrating the recent trials, we and others recognize that scientific success is but the first step, and successful implementation is the next critical step to realize the benefits for our patients.[3,4] Furthermore, there remains a need for fundamental mechanistic understanding of the central vs. peripheral (skeletal muscles, kidneys) effects of SGLT inhibitors and iron in HF with both reduced and preserved LVEF; as well as an unmet clinical need to identify biological markers or surrogate outcomes to help guide treatment choices and identify which patients might benefit most from these new treatment options. With improved patient outcomes, we may move away from the term 'failure' to renaming the syndrome of HF in terminology that optimally reflects successful strides taken and new hope for our patients.[10]

Conflict of interest: J.T. reports speaker fees from Roche diagnostics. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Abbott Diagnostics, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Biofourmis, Boehringer Ingelheim, Boston Scientific, Corvia Medical, Cytokinetics, Darma Inc., Us2.ai, JanaCare, Janssen Research & Development LLC, Medtronic, Menarini Group, Merck, MyoKardia, Novartis, Novo Nordisk, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, Stealth BioTherapeutics, The Corpus, Vifor Pharma and WebMD Global LLC, and serves as co-founder and non-executive director of Us2.ai. K.T. has nothing to declare.

References

1. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
2. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
3. Bhatt DL, Verma S, Braunwald E. The DAPA-HF trial: a momentous victory in the war against heart failure. *Cell Metab* 2019;**30**:847–849.
4. Felker GM. Building the foundation for a new era of quadruple therapy in heart failure. *Circulation* 2020;**141**:112–114.
5. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sørensen T, Böhm M, Bonderman D, Cleland JGF, Corbalan R, Crespo-Leiro MG, Dahlström U, Echeverria LE, Fang JC, Filippatos G, Fonseca C, Goncalvesova E, Goudev AR, Howlett JG, Lanfear DE, Li J, Lund M, Macdonald P, Mareev V, Momomura S-I, O'Meara E, Parkhomenko A, Ponikowski P, Ramires FJA, Serpytis P, Sliwa K, Spinar J, Suter TM, Tomcsanyi J, Vandekerckhove H, Vinereanu D, Voors AA, Yilmaz MB, Zannad F, Sharpsten L, Legg JC, Varin C, Honarpour N, Abbasi SA, Malik FI, Kurtz CE, GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med* 2020;**384**.
6. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Göhring UM, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, Comin-Colet J, von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie HJ, Motro M, Butler J, Friede T, Jensen KH, Pocock S, Jankowska EA, AFFIRM-AHF investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* 2020;**S0140-6736**:32339–32334.
7. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B, SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2020;**384**:117–128.
8. Bromage DI, Cannatà A, Rind IA, Gregorio C, Piper S, Shah AM, McDonagh TA. The impact of COVID-19 on heart failure hospitalization and management: report from a Heart Failure Unit in London during the peak of the pandemic. *Eur J Heart Fail* 2020;**22**:978–984.
9. Lam CSP, Butler J. Victims of success in failure. *Circulation* 2020;**142**:1129–1131.
10. Peterson PN, Allen LA, Heidenreich PA, Albert NM, Piña IL, American Heart Association. The American Heart Association Heart Failure Summit, Bethesda, April 12, 2017. *Circ Heart Fail* 2018;**11**:e004957.

Authors



Biography: Dr Teramoto is a clinical cardiologist at St. Marianna University School Medicine Hospital, Kanagawa, Japan. She received MD and PhD from St. Marianna University School of Medicine and also MPH from Harvard T. H. Chan School of Public Health. She was a former research fellow at Cardiovascular Imaging Laboratory at Brigham and Women's Hospital, Boston, USA. Her interests are in clinical research on the diagnosis, treatment, and prevention of heart failure.

Biography: Dr Tromp is a physician with a strong interest in public health and heart failure in lower- and middle-income countries. He completed his MD and PhD at the University of Groningen, the Netherlands. He currently work as a research fellow at the National Heart Centre Singapore and is co-director of the Cardiovascular Clinical Trial Data Management Centre. His research focuses on global epidemiology of heart failure, with a special interest in treatment and prevention in lower- and middle-income countries.

Biography: Dr Lam is a Senior Consultant at NHCS specializing in heart failure and recognized globally for expertise in heart failure with preserved ejection fraction. She is a recipient of the NMRC Senior Investigator Clinician Scientist Award, Programme Lead of A*STaR's Asian neTwork for Translational Research and Cardiovascular Trials (ATTRaCT), Principal Investigator of ASIAN-HF (multinational study across 11 Asian countries), and Steering Committee member of multiple global clinical trials. She has published >200 articles in journals including *NEJM*, *JAMA*, *Lancet*, *Circulation*, and *European Heart Journal*. She serves as Associate Editor for *Circulation* and the *European Journal of Heart Failure*. Dr Lam is heard weekly on the global podcast 'Circulation On The Run' and seen regularly on television as the Resident Doctor of 'Body and Soul' by MediaCorp Singapore.