Cardiac Biomarkers in Advanced Heart Failure: How Can They Impact Our Pre-transplant or Pre-LVAD Decision-making

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Abstract

Purpose of Review Decision-making in advanced heart failure (HF) is a complex process that involves careful consideration of competing tradeoffs of risks and benefits in regard to heart transplantation (HT) or left ventricular assist device (LVAD) placement. The purpose of this review is to discuss how biomarkers may affect decision-making for HT or LVAD implantation.
Recent Findings N-Terminal probrain natriuretic peptide, soluble suppression of tumorigenicity-2, galectin-3, copeptin, and troponin T levels are associated with HF survival and can help identify the appropriate timing for advanced HF therapies. Patients at risk of right ventricular failure after LVAD implantation can be identified with preimplant biomarkers of extracellular matrix turnover, neurohormonal activation, and inflammation.
Summary There is limited data on the adoption of biomarker measurement for decision-making in the allocation of advanced HF therapies. Nonetheless, biomarkers can improve risk stratification and prognostication thereby optimizing patient selection for HT and LVAD implantation.

Keywords Decision-making · Heart transplant · Heart failure · Ventricular assist device

Abbreviations

ADHF	Acute decompensated heart failure
ADHERE	Acute Decompensated National Heart Failure Registry
ATTEND	Acute decompensated heart failure syndromes
Bio-SHiFT	Role of Biomarkers and Echocardiography in Prediction of Prognosis of Chronic Heart Failure Patients
COACH	Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
CRT-D	Cardiac resynchronization therapy-defibrillators
GALLANT	Neutrophil gelatinase-associated lipocalin evaluation along with brain natriuretic peptide in acutely decompensated heart failure
GDF-15	Growth differentiation factor 15
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure
HF	Heart failure
HF-ACTION	Heart failure: a controlled trial investigating outcomes of exercise training
LVAD	Left ventricular assist device
MOLITOR	Impact of therapy optimization on the level of biomarkers in patients with acute and decompensated chronic heart failure

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NGAL	Neutrophil gelatinase-associated lipocalin
NT-proBNP	N-Terminal pro brain natriuretic peptide
PRAISE-2	Prospective Randomized Amlodipine Evaluation 2
PROSE-ICD	Prospective Observational Study of Implantable Cardioverter-Defibrillators
sST2	Soluble suppression of tumorigenicity-2
Val-HeFT	Valsartan Heart Failure trial

Introduction

Risk stratification in advanced heart failure (HF) is a complex process that involves appropriate identification of patients that would benefit from advanced therapeutic interventions in tandem with risk assessment and patient values [1, 2]. Due to the progressive but nonlinear trajectory of advanced HF [3], it is important for clinicians to recognize the appropriate timing of advanced therapies. Although risk stratification is an integral part of the decision-making process in advanced HF [4], prognostication in HF care is difficult [5]. Under ideal circumstances, most prognostic HF models have modest accuracy [6]. Biomarkers have the potential to improve risk stratification [7] and help medical professionals identify when the patient is medically appropriate for advanced HF therapies. The goals of this review are to discuss how biomarkers may enhance risk stratification and impact decision-making for advanced HF therapies. This review will also focus on biomarkers that can be used to forecast right ventricular failure after left ventricular assist device (LVAD) implantation.

Candidate Selection for Heart Transplant Versus Left Ventricular Assist Device: Do Biomarkers Have a Role?

The role of biomarkers in decision-making for advanced HF is understudied. Currently, biomarkers are routinely used for prognostication and confirmation of advanced disease. The utility of multiple biomarkers that reflect different pathophysiological pathways are increasingly being explored in HF risk stratification. Metabolic biomarkers like insulin-like growth factor 1 may be higher after heart transplantation when compared with LVAD placement and could influence rehabilitative outcomes after surgery [8]. However, there is currently no evidence to demonstrate that biomarkers can distinguish patients that will perform better with either therapy.

Biomarkers and Heart Failure Severity

HF is a clinical syndrome that is characterized by complex heterogenous pathological pathways that all contribute to the development and progression of the disease. From a conceptual framework, biomarkers can be classified into the following categories: inflammatory, neurohormonal, myocardial stretch, myocardial injury, myocardial remodeling/fibrosis, renal injury, and oxidative stress. Biomarkers are prognostic indicators in HF and help to identify patients with severe disease (Table 1).

Myocyte Stress and Stretch

Brain Natriuretic Peptide and NT-Pro Brain Natriuretic Peptide
NT-proBNP and BNP are produced from a precursor peptide which is secreted from the cardiac ventricles in response to volume expansion, pressure overload, and increase in wall tension [12, 34•]. Admission NT-proBNP levels > 5000 pg/mL were associated with death and markedly discriminated advanced HF candidates for LVAD implantation or urgent heart transplantation [12]. In the Role of Biomarkers and Echocardiography in Prediction of Prognosis of Chronic HF Patients (Bio-SHiFT) study, increases in serial NT-proBNP levels were associated with worsening New York Heart Association class and independently predicted cardiac death, heart transplantation, LVAD implantation, or HF hospitalization in the outpatient setting [34•]. A single measurement of NT-proBNP in advanced HF patients is helpful in identifying patients who are at the highest risk of death and is a better prognostic marker than left ventricular ejection fraction, peak oxygen consumption, or the HF survival score [35]. BNP improves the prognostic information obtained from cardiopulmonary exercise testing. Patients with a peak oxygen consumption of 10 to 14 mL/min/kg and low BNP (< 506 pg/mL) had a VAD-free or heart transplant–free survival similar to post-transplant survival in heart transplant recipients (1-year survival: 90.8% versus 87.2%) [9]. In hospitalized HF patients, persistently elevated BNP levels despite maximal guideline-directed medical therapy was significantly associated with elevated risks of 180-day mortality when compared with improved BNP levels (26.4% vs 13.2%, $p < 0.0001$) [36]. For each 100-pg/mL increase in BNP amongst HF patients, there was an associated 35% increase in the relative risk of death [34•]. Despite the overwhelming evidence for the use of BNP in HF (as well as the strong guideline recommendations), it has not been consistently identified as indicator for early referral for LVAD therapy amongst HF providers [37].

BNP enhances risk stratification when used in combination with different HF risk models. In a single-center, retrospectively defined, HF cohort with reduced ejection fraction, use of the Seattle HF model and BNP risk-stratification algorithm demonstrated that irrespective of a patient's predicted risk

Table 1 Biomarkers for risk prediction in advanced heart failure

Biomarker	Endpoints	Publication date, author	Sample size	Main findings/results
Myocyte stretch and stress				
BNP	VAD-free or HTx-free survival	2013, Kato [9]	424	Peak VO_2 of 10 to 14 mL/min/kg and low BNP (< 506 pg/mL) was associated with VAD-free or HTx-free survival similar to post-transplant survival in HTx recipients.
	Death, urgent HTx, or LVAD implantation	2014, Chyu [10]	2255	UCLA risk score was a strong risk discriminator with C-indices ≥ 0.8 in both men and women.
	1-year survival free of HTx or LVAD	2016, Abouezzedine [11]	441	BNP ≥ 700 pg/mL identified patients with ≥ twofold mortality risk irrespective of SHFM and BNP < 700 pg/mL identified patients that the SHFM risk was well calibrated.
NT-proBNP	Mortality, HT, or LVAD implantation	2004, Rothenburger [12]	550	NT-proBNP > 5000 pg/mL is associated with death and need for LVAD implantation or urgent HTx
	1-year mortality	2013, Scrutinio [13]	541	NT-proBNP significantly improved ADHF/NT-proBNP score, NRI (0.129; $p = 0.0027$) and IDI (0.037; $p = 0.005$); C-index was 0.839.
sST2	Death or HF hospitalization Death, HTx or LVAD placement	2019, Najjar [14]	193	sST2 is associated with death and with death or hospitalization in HFpEF and with death, HTx. or LVAD placement in HFrEF.
GDF-15	All-cause mortality	2017, Sharma [15]	910	Doubling of GDF-15 levels was associated with a 30% increase in the risk of all-cause mortality.
Fibrosis and remodeling				
Galectin-3	All-cause mortality and hospitalizations during follow-up	2013, van der Velde [16]	1653	Increases, either 15% increase or increase from below to above 17.8 ng/mL in galectin-3, were associated with worse prognosis than stable or decreasing levels.
	All-cause mortality, HTx, or VAD placement	2016, French [17]	5011	Elevated galectin-3 levels were associated with increased risk of all-cause mortality, HTx, or VAD placement.
	All-cause death, HTx, and HF rehospitalization	2016, Feola [18]	83	Pre-discharge value of galectin-3 (≥ 17.6 ng/mL) and BNP (≥ 500 pg/mL) was a significant predictor of cardiac deaths and rehospitalizations.
Inflammation				
CRP	All-cause and cardiac and non-cardiac death	2017, Minami [19]	4777	Markedly elevated CRP levels at admission are associated with higher short-term cardiac and non-cardiac mortalities.
Neurohormonal activation				
Copeptin	Death, HTx, or LVAD placement	2017, Zabarovskaja [20•]	63	Copeptin independently predicts death, HTx, or LVAD implantation in AHF
Renal injury				
NGAL	Death, hospital admissions, or emergency room visits	2011, Maisel [21]	196	Risk of adverse outcomes is greatest when both elevated NGAL (> 100 ng/mL) and BNP (> 330 pg/mL) are present.
		2013, Alvelos [22]	121	

Table 1 (continued)

Biomarker	Endpoints	Publication date, author	Sample size	Main findings/results
	Death or hospital admission			Admission NGAL > 167.5 ng/mL predicted a 3-fold increase in morbidity and mortality within 3 months of an ADHF admission.
	All-cause mortality	2014, van Deursen [23]	562	NGAL predicted HF mortality better than established renal function indices
Cystatin C	Cardiac death or 60-day readmission for ADHF	2015, Rafouli-Stergiou [24]	96	Cystatin C ≥ 0.4 mg/L is associated with a 45% higher risk of cardiac death or rehospitalization at 60 days.
Oxidative stress				
Uric acid	Death, HTx-free, or LVAD-free survival	2006, Levy [25]	1125	Model predicted 1- and 2-year survival rates of 73.4% and 56.7% versus actual survival of 74.3% and 56.0%; correlation between predicted and actual survival was 0.97.
	All-cause death or cardiovascular hospitalization	2018, Mantovani [26]	6683	Elevated uric acid level > 7.2 mg/dL is associated with poor long-term survival and cardiovascular hospitalization.
Multi-marker models				
Cystatin C, NT-proBNP	All-cause mortality	2007, Lassus [27]	620	Risk of all-cause mortality at 12 months was 5% in the lowest tertile and 49% in the highest tertile for both biomarkers
Troponin, BNP	In-hospital mortality	2008, Fonarrow [28]	42,636	Combination of elevated troponin levels and BNP > 840 pg/mL had the highest risk of mortality
Cystatin C, troponin T, NT-proBNP	Mortality and/or HF admission	2009, Manzano-Fernandez [29]	145	Gradual increase in risk of mortality and/or HF readmissions as number of elevated biomarkers increased
NT-proBNP, sST2	Death or HTx	2011, Ky [30]	1141	Elevated sST2 was associated with an increased risk of death or HTx; addition of sST2 and NT-proBNP to SHFM improved risk discrimination in HF patients.
Copeptin, BNP, hs-TnT	All-cause mortality or ADHF	2011, Tentzeris [31]	172	Addition of copeptin to NT-proBNP and hs-cTnT resulted in significant improvement in prediction of events, NRI (0.208; $p < 0.05$)
Troponin T, hs-CRP	All-cause mortality, HTx, or LVAD implantation	2015, Nauffal [32]	1189	HF–CRT score identified patients at high, intermediate, or low risk of death or in need for advanced circulatory support within 3 years of CRT-D implantation
GDF-15, BNP	All-cause mortality	2018, Bettencourt [33]	158	2-year mortality risk increased over fourfold, when GDF-15 and BNP were both elevated

ADHF, acute decompensated heart failure; AHF, advanced heart failure; C-index, concordance statistic; CRT-D, cardiac resynchronization therapy-defibrillator; GDF-15, growth differentiation factor-15; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-cTn, high-sensitivity cardiac troponin; hs-CRP, high sensitivity C-reactive protein; HTx, heart transplant; IDI, integrated discrimination index; LVAD, left ventricular assist device; NGAL, neutrophil gelatinase-associated lipocalin; NRI, net reclassification index; NT-proBNP, N-terminal proBrain natriuretic peptide; SHFM, Seattle heart failure model; sST2, soluble suppression of tumorigenicity-2; VO₂, oxygen consumption; UCLA, University of California, Los Angeles

category, BNP ≥ 700 pg/mL identified patients with greater than twofold mortality risk than the Seattle HF model would indicate while BNP < 700 pg/mL identified patients that the Seattle HF model was well calibrated [11]. The acute decompensated HF/NT-proBNP (ADHF/NT-proBNP) risk score provides a long-term grading of HF-related risk that could impact decision-making [4] for advanced therapies in hospitalized patients. Long-term (up to 36 months) survival steadily declined with increasing ADHF/NT-proBNP score [4]. Although the mortality risk was greatest in the first 12 months, patients in the highest risk category still had > 3-fold excess risk of death beyond 12 and 24 months after admission when compared with those in the lowest risk category [4]. The University of California, Los Angeles risk score, a 4-variable model that includes BNP, oxygen consumption, New York Heart Association class, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use provides better distinction of HF-related risk than the Seattle HF model and HF survival score [38].

Soluble Suppression of Tumorigenicity 2 Soluble suppression of tumorigenicity 2 (sST2) is a member of the interleukin-1 family [34•] and is linked with myocardial stress [14•], remodeling [39], and neurohormonal activation [40] in advanced HF patients. sST2 concentrations provide incremental value (and may be superior) to natriuretic peptides for HF prognostication [41], and chronically elevated or rising levels strongly predict adverse outcomes [42]. sST2 is associated with death or hospitalization in HF with preserved ejection fraction, and with death, heart transplantation or LVAD implantation in HF with reduced ejection fraction; HR (95% CI) of 6.62 (1.04–42.28), and 3.51 (1.05–11.69) respectively [14•]. In the Penn HF study, sST2 was strongly associated with HF severity [30], and patients with elevated levels had a markedly increased risk of death or heart transplantation [30]. Amongst NYHA class III to IV HF patients, changes in sST2 levels were independent predictors of subsequent mortality or heart transplantation in the Prospective Randomized Amlodipine Evaluation 2 (PRAISE-2) trial [40]. Failure of sST2 to drop by 15% during a HF hospitalization or by 25% on serial measurements in the outpatient setting at least 2 weeks apart was associated with an increased risk of death at 90 days and adverse outcomes, respectively [43]. The addition of sST2 and NT-proBNP levels to the Seattle HF model improved risk discrimination and reclassified 14.9% of HF patients into more appropriate categories in the Penn HF study [30]. Although sST2 has a strong independent predictive value for all-cause mortality, cardiovascular mortality, and HF hospitalization, and provides additive prognostic value to NT-proBNP and high sensitivity troponin T [39], it is not routinely measured or considered when making therapeutic decisions on heart transplantation or LVAD implantation in advanced HF patients.

Growth Differentiation Factor-15 Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor-β family is secreted from cells such as adipocytes and myocytes in response to cellular ischemia, mechanical strain, and oxidative stress [15]. In the Valsartan HF trial (Val-HeFT), GDF-15 levels were linked to several pathological processes that are associated with HF severity and progression, including neurohormonal activation, inflammation, myocyte death, and renal dysfunction [44]. Circulating GDF-15 levels are related to adverse cardiovascular outcomes and survival independently of established clinical and biochemical risk markers in both HF with preserved ejection fraction and HF with reduced ejection fraction [44–46]. Doubling of GDF-15 levels was associated with a 30% increase in the risk of all-cause mortality in the HF: a controlled trial investigating outcomes of exercise training (HF-ACTION) [15]. The prognostic utility of GDF-15 increases when combined with other biomarkers. After a hospital admission for ADHF, the 2-year mortality risk increases over fourfold, when GDF-15 and BNP are both elevated at discharge [33].

Myocyte Injury

Troponin and High-Sensitivity Troponin Cardiac troponins are elevated in patients with myocardial damage due to ischemia, inflammation, and mechanical stress [34•]. Elevated troponin I is associated with worsened clinical profiles and impaired hemodynamics in advanced HF patients undergoing heart transplant evaluation [47]. Doubling of high-sensitivity troponin T levels independently predicted an increased risk of all-cause death by 48%, cardiovascular death by 40%, and cardiovascular hospitalization by 42% in chronic HF patients [48]. A high-sensitivity troponin T value of 18 ng/L was the cutoff for prediction of all-cause death [48]. High-sensitivity troponin T may have a better prognostic value than NT-proBNP and high-sensitivity C-reactive protein, and its addition to NT-proBNP significantly improved risk categorization for all-cause death by 46%, cardiovascular-related mortality by 26%, and HF hospitalization by 28% [49]. In the Acute Decompensated National HF Registry (ADHERE), admission levels of troponin and BNP were significant independent predictors of mortality in ADHF; patients with elevated troponin levels and BNP > 840 pg/mL had the highest risk of mortality [28]. In HF patients with cardiac resynchronization therapy-defibrillators (CRT-D), a simple score (HF-CRT score) combining baseline clinical and biomarker values (troponin T and high-sensitivity C-reactive protein) identified patients at high (score 4–5), intermediate (score 2–3), or low (score 0–1) risk of death or need for advanced circulatory support within 3 years of CRT-D implantation in the Prospective Observational Study of Implantable Cardioverter-Defibrillators (PROSE-ICD) [32]. For instance, a HF-CRT score of ≥ 4 conferred a 64.8% probability of mortality or need

for advanced circulatory support [32]. Measurement of troponin is recommended to establish prognosis on hospital admission for ADHF in the 2017 HF guidelines [7] and could potentially influence the timing for initiation for advanced therapies.

Fibrosis and Remodeling

Galectin-3 Galectin-3 is a soluble β-galactoside-binding lectin released by activated cardiac macrophages that binds to and activates fibroblasts, forming collagen which plays an integral role in myocardial fibrosis [17•]. Elevated galectin-3 levels were associated with increased risk of all-cause mortality, heart transplantation, or VAD placement among participants enrolled in the Penn HF study [17•] In the Controlled Rosuvastatin Multinational trial in HF (CORONA) and Coordinating Study Evaluating Outcomes of Advising and Counseling in HF (COACH), patients who had an increase, either a 15% increase or an increase from below to above 17.8 ng/mL in galectin-3 levels, had a profoundly worse prognosis than those with stable or decreasing levels [16]. In elderly HFrEF patients hospitalized for ADHF, a pre-discharge value of galectin-3 (≥ 17.6 ng/mL) combined with BNP (≥ 500 pg/mL) were predictors of cardiac mortality and rehospitalization [18].

Renal Injury

Renal impairment is associated with adverse outcomes in HF. Besides the commonly used markers of renal function such as blood urea nitrogen and serum creatinine, both of which have prognostic implications, newer biomarkers for renal injury have emerged. Biomarkers of renal injury provide crucial information for decision-making in advanced HF by identifying patients with kidney disease. End-stage renal disease at the time of LVAD implantation is associated with poor prognosis, with most patients surviving less than 3 weeks [50]. Consequently, chronic kidney disease is considered a relative contradiction for LVAD placement and chronic hemodialysis therapy is considered an absolute contraindication to destination-LVAD therapy [51]. Irreversible renal dysfunction identifies candidates who may require dual organ transplantation with a heart and kidney instead of isolated heart transplantation.

Neutrophil Gelatinase-Associated Lipocalin Neutrophil gelatinase-associated lipocalin (NGAL) is a member of the lipocalin family of proteins that are released from the kidney following ischemic or nephrotoxic injury [21, 52]. NGAL levels correlate with impairment of kidney function [22, 53, 54]. Elevated urine [52] and plasma [22, 54] NGAL levels are predictors of HF rehospitalization and/or death when measured at the time of admission for ADHF. Serum NGAL

admission levels > 167.5 ng/mL predicted an almost 3-fold increase in morbidity and mortality within 3 months of admission for ADHF in an elderly cohort of HF patients [22]. In the COACH trial, plasma NGAL levels predicted HF mortality, both amongst patients with and without chronic kidney disease, and were a stronger predictor of mortality than established renal function indices such as the estimated glomerular filtration rate and cystatin C [23]. In the NGAL evaluation along with BNP in acutely decompensated HF (GALLANT) trial, plasma NGAL at the time of hospital discharge was a strong predictor of 30-day outcomes in patients admitted with acute HF, outperforming BNP, and substantially superior to conventional measures of renal function [21]. The risk of adverse outcomes (death, hospital readmissions, or emergency room visits) was greatest when elevated NGAL (> 100 ng/mL) and BNP (> 330 pg/mL) were both present, (HR (95% CI), 16.9 (2.3–195.9)) [21]. Given the critical importance of renal function in guiding selection of suitable candidates for destination-LVAD therapy, NGAL may be a useful component of routine pre-LVAD testing.

Cystatin C Cystatin C is an endogenous cysteine proteinase inhibitor that is produced by nucleated cells, freely filtered by the glomerulus, and neither secreted nor reabsorbed by the renal tubules [55]. It is a sensitive marker for measuring renal function [54]. Cystatin C has been identified as a predictor of all-cause mortality and rehospitalization for HF patients [27]. In hospitalized advanced HF patients, a cystatin C level ≥ 0.4 mg/l was associated with a 45% higher risk of cardiac death or rehospitalization at 60 days [24]. Adverse events such as cardiac-related death, HF progression requiring hospitalization for intravenous therapy or heart transplantation was more common amongst heart failure with reduced ejection fraction patients who had greater cystatin C levels [56]. Cystatin C offers superior prognostic information than conventional markers of renal function such as creatinine, and the modification of diet in renal disease equation [27, 29]. In ADHF patients, the cystatin C–based chronic kidney disease epidemiology collaboration equations were superior to the modification of diet in renal disease equations for predicting mortality and/or HF hospitalization especially in patients with glomerular filtration rate > 60 mL min^{-1} 1.73 m^{-2} [57]. The simultaneous use of cystatin C and other biomarkers improves HF risk stratification. In a study including cystatin C, NT-proBNP, and troponin T, there was a gradual increase in the risk of mortality and/or HF readmissions as the number of elevated biomarkers increased; 25.8%, 37.1%, 43.6%, and 66.7% of participants reached the endpoint for 0, 1, 2, and 3 elevated biomarkers, respectively, p for trend = 0.015 [29]. In another study that combined tertiles of cystatin C and NT-proBNP, the risk of all-cause mortality at 12 months was 5% in the lowest tertile and 49% in the highest tertile for both biomarkers [27].

Inflammation

Systemic inflammation is an important risk factor and driver of adverse outcomes in HF [58, 59]. Elevated inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-α are associated with increasing morbidity and mortality in chronic HF of both ischemic and non-ischemic etiologies [59].

C-reactive Protein C-reactive protein is produced predominantly by hepatocytes under the influence of cytokines such as interleukin-6 and tumor necrosis factor-α [60]. The utility of C-reactive protein as a HF marker is hampered by the concomitant occurrence of infection which is common in decompensated states [59]. In the ADHF syndromes (ATTEND) registry, markedly elevated C-reactive protein levels at admission were associated with greater short-term cardiac and noncardiac mortalities in advanced HF patients [19]. Elevated levels of high-sensitivity C-reactive protein is also associated with poor outcomes in HF patients with severe systolic and diastolic dysfunction [60]. In the Bio-SHiFT study, temporal patterns representing the evolution of levels and rate of change in both C-reactive protein and NT-proBNP were associated with adverse prognosis in patients with chronic HF [61]. In multi-marker models evaluating the prognostic ability of four biomarkers (C-reactive protein, sST2, NT-proBNP, and high-sensitivity troponin T), C-reactive protein and sST2 provided the best risk stratification for all-cause mortality and cardiovascular mortality in HF patients [58].

Neurohormonal Activation

Copeptin Copeptin is the C-terminal fragment of the precursor of arginine vasopressin which is released from the posterior pituitary gland in response to decreases in plasma volume and increased serum osmolality [62]. Copeptin is a predictor of mortality in HF [20•, 62, 63]. Copeptin independently predicted death, heart transplantation, or LVAD implantation in advanced HF patients (HR (95% CI), 3.28 (1.66–6.50)) and was correlated with markers of hemodynamics and congestion [20•]. In the impact of therapy optimization on the level of biomarkers in patients with acute and decompensated chronic HF (MOLITOR) [64] and biomarkers in acute HF (BACH) [65] studies, copeptin was a predictor of both 90-day mortality and hospital readmissions. Copeptin provides similar or superior prognostic information to BNP [63], and when combined with BNP, it offers additional prognostic information for both all-cause and cardiovascular mortality [62]. Copeptin provides greater prognostic information for HF mortality when combined with sodium (net reclassification index (NRI), 27.4%; $p < 0.001$), and when both sodium and copeptin are added to NT-proBNP (NRI, 32.7%; $p < 0.001$) [65].

The combination of copeptin and high-sensitivity troponin T provides a graded association with impaired clinical outcomes in HF patients which is independent of NT-proBNP, (HR (95% CI), 1.40 (1.20–1.70)) [31]. The addition of copeptin to risk models containing NT-proBNP and high-sensitivity troponin T provides improved prediction of all-cause mortality or HF hospitalization (NRI, 20.8%; $p < 0.05$) [31].

Oxidative Stress

Uric Acid Hyperuricemia in HF results from increased uric acid production due to upregulation of xanthine oxidase, a source of free radicals which stimulates proinflammatory pathways and contributes to oxidative stress and endothelial dysfunction in the heart [66]. Hyperuricemia has been identified as a risk factor for HF readmissions and/or mortality in multiple studies [26, 66]. In the Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-HF (GISSI-HF) trial, patients with uric acid levels > 7.2 mg/dL had a greater risk of all-cause death, cardiovascular death, and cardiovascular hospitalization compared with those with lower values [26]. The relationship between uric acid and HF mortality is incremental; patients with levels < 400 μmol/L (normal), 401–600 μmol/L, 601–800 μmol/L, and > 800 μmol/L had survivals of 93%, 87%, 54%, and 17%, respectively ($p < 0.0001$) [67]. Serum uric acid and the HF survival score are both independent predictors of HF prognosis [67]. Furthermore, uric acid improves the positive and negative discriminatory power of the HF survival score [67].

Biomarkers and Outcomes After Advanced Heart Failure Therapies

Biomarkers are valuable in decision-making for advanced HF therapies because they can help identify patients who are at increased risks of poor outcomes post-operatively. Identification of potential complications after LVAD implantation is often challenging. Elevated soluble suppression of tumorigenicity-2 (sST2) [68] and interleukin-6 [69] levels at the time of LVAD implantation have been associated with an increased risk of developing multiorgan failure post-operatively. Elevated BNP levels before LVAD implantation correlates with the occurrence of ventricular arrhythmias post-operatively [70]. Although biomarkers are useful in identifying advanced HF patients that need heart transplantation, it is unclear if circulating pre-transplant biomarker levels have important prognostic significance immediately after transplant. Pre-transplant galectin-3 [71] has been associated with cardiac allograft vasculopathy development in heart transplant recipients.

Predicting Right Ventricular Failure After LVAD Implantation

Right ventricular failure is an important complication of advanced HF that adversely affects outcomes after LVAD therapy [3]. Right ventricular failure has a prevalence of 4 to 50% in LVAD patients [72] and is associated with increased morbidity [3, 73] and a mortality rate as high as 29% 6 months after implantation [72]. The identification of potential LVAD patients who are at high risk of right ventricular failure is challenging [74]. The Michigan-right ventricular failure risk prediction score which incorporates biomarkers of renal and hepatic dysfunction provides the greatest discrimination for predicting right ventricular failure ($C = 0.74$ (95% CI, 0.61–0.87)) and in-hospital mortality ($C = 0.67$ (95% CI, 0.52–0.83)) after LVAD implantation [74]. It is important to recognize LVAD candidates with severe isolated right ventricular or biventricular failure pre-operatively because they may require biventricular assist devices or total artificial heart support [72]. Persistently elevated markers of extracellular matrix turnover (osteopontin, tissue inhibitors of matrix metalloprotein-1, and matrix metalloprotein-2) [75], neurohumoral activation (endothelin-1, NT-proBNP), inflammation (neopterin, procalcitonin) [76], and neutrophil gelatinase-associated lipocalin (NGAL) [53] identify advanced HF patients who will likely develop right ventricular failure after LVAD implantation. Specifically, preimplantation osteopontin levels > 259.2 ng/mL predict the development of right ventricular failure after LVAD implantation [75]. However, many of these markers of right ventricular failure after LVAD implantation reflect target organ dysfunction and are not specific to the right ventricle.

Emerging Biomarkers for Decision-making in Advanced Heart Failure Patients

Biomarker discovery can be accelerated by combining automated clinical biobanking with proteomics [77•]. Angiopoietin-2 and thrombospondin-2 have been shown to provide incremental diagnostic utility to BNP for acute HF using proteomic analysis [77•] and both were appropriately decreased after heart transplantation and LVAD implantation [77•]. These novel markers could potentially yield useful information on the appropriate timing for initiation of advanced therapies in end stage HF patients.

Future Directions

To optimize the utility of biomarkers for decision-making in advanced HF, further studies are needed to clearly define acceptable cutoff levels which should be standardized across laboratories. Biomarkers that offer the greatest utility for risk stratification should be identified. The effects of adopting a multi-marker strategy based on the most useful biomarkers into the routine evaluations of advanced HF patients should be investigated.

Conclusions

Although biomarkers offer the promise of improving HF risk stratification, they are not routinely considered during decision-making for heart transplantation or LVAD implantation in advanced HF patients. Biomarkers could influence decision-making on advanced therapies by predicting patients who are at high risk for LVAD-related complications like right ventricular failure and multiorgan failure. A risk assessment strategy utilizing multiple biomarkers provides better prognostic information than the use of an individual marker.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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