THE AMERICAN JOURNAL of MEDICINE®

Coronary Artery Disease in Patients with Heart Failure: Incidental, Coincidental, or a Target for Therapy?

The prevalence of heart failure in the US and globally continues to increase[1] at a rate faster than the rate at which we expand our knowledge and understanding of this complex entity. Pharmacologic therapies targeting ventricular remodeling have contributed to incremental reductions in morbidity and mortality among ambulatory heart failure patients, primarily among those with reduced ejection fraction.[2] Unfortunately, the total number of US hospitalizations for heart failure has remained essentially unchanged over the last decade.[3] The majority of patients with established heart failure have comorbid obstructive coronary artery disease or traditional coronary heart disease risk factors.[4] Great strides have been made in the treatment, overall care patterns, and outcomes of patients with coronary artery disease alone. Thus, translating these well-established aggressive therapies of ischemic heart disease to patients with heart failure holds significant promise. Patients with ischemic etiology for heart failure are at higher risk of adverse outcomes compared to their nonischemic counterparts in both inpatient[5] and outpatient[6] settings. However, whether the additional risk related to coronary artery disease among heart failure patients can be lowered by noninvasive and invasive strategies is unclear and is debated.

Until recently, the treatment of coronary artery disease and ischemia in heart failure patients has been largely empiric, with the expectation that the benefits demonstrated with therapies in patients with coronary artery disease without heart failure would apply to those with heart failure as well. The most recent iteration of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines highlights this uncertainty but continues to advocate for the routine evaluation and management of coronary artery disease in select heart failure populations (**Table**).[7] National performance measures for comorbid coronary artery disease apply across cardiovascular populations, including those with heart failure. In the last decade, however, a number of landmark clinical trials have provided critical data mandating re-examination of coronary artery disease management in heart failure patients.[8]

SELECT TARGETS

Traditional metrics and risk factors used to guide the treatment of coronary artery disease may not be applied readily to patients with heart failure. Serum lipid levels are inversely associated with outcomes in hospitalized patients and outpatients with heart failure.[9] Higher body mass index is associated with improved mortality and hospitalization risk, even in patients with relatively early-stage heart failure.[10] Similarly, systolic blood pressure represents a strong inverse predictor of postdischarge outcomes in patients hospitalized for heart failure at the time of admission[11] and after stabilization.[12] Prostaglandins and prostacyclins, potent vasodilatory hormones that are inhibited by aspirin, may counterbalance the negative effects of circulating neurohormones in patients with heart failure.[13] The presence of viable, but dysfunctional, myocardium has not been independently associated with outcomes in patients with heart failure and severely reduced ejection fraction, when adjusted for other comorbidities.[14] Similarly, inducible myocardial ischemia as assessed by noninvasive stress testing and quantification of jeopardized myocardium has not been universally predictive of adverse clinical end points in this population.[15]

THE TREATMENTS

A number of effective pharmacotherapies in the current chronic heart failure armamentarium target coronary artery disease. In fact, mainstays of chronic heart failure regimens, including angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, have been shown to reduce rates of myocardial infarction and cardiovascular death in patients

Funding: None.

Conflicts of Interest: GCF: Research Support: NIH (significant), AHRQ (significant); Consultant: Novartis (significant), Medtronic (modest), Bayer (modest), Gambro (modest), Janssen (modest). JB: Research Support: National Institutes of Health, European Union, Health Resource Services Administration, Food and Drug Administration; Consultant: Amgen, Bayer, Celladon, Gambro, GE Healthcare, Janssen, Medtronic, Novartis, Ono, Relypsa, Trevena. MG: Consultant: Abbott Labs, Astellas, AstraZeneca, Bayer Schering PharmaAG, CorThera Inc., Cytokinetics Inc., DebioPharm S.A., Errekappa Terapeutici (Milan, Italy), Glaxo Smith Kline, JNJ, Medtronic, Novartis Pharma AG, Otsuka, Sigma Tau, Solvay Pharmaceuticals, and Pericor Therapeutics. The rest of the authors disclose no conflicts of interest related to this work.

Authorship: All authors had access to the data and a role in writing the manuscript.

http://dx.doi.org/10.1016/j.amjmed.2014.01.041

Table ACC/AHA Guideline Recommendations Regarding CAD Management in Patients with Heart Failure

Heart Failure Population	Recommendation	Class	Level of Evidence
Initial evaluation	Initial laboratory evaluation with serum lipid profile	I	C
	Coronary arteriography should be performed in patients presenting with HF who have angina or significant ischemia unless the patient is not eligible for revascularization of any kind.	I	C
	Coronary arteriography is reasonable for patients presenting with HF who have chest pain that may or may not be of cardiac origin who have not had evaluation of their coronary anatomy and who have no contraindications to coronary revascularization.	IIA	C
	Coronary arteriography is reasonable for patients presenting with HF who have known or suspected coronary artery disease but who do not have angina unless the patient is not eligible for revascularization of any kind.	IIA	C
	Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with HF who have known coronary artery disease and no angina unless the patient is not eligible for revascularization of any kind.	IIA	B
	Noninvasive imaging may be considered to define the likelihood of coronary artery disease in patients with HF and LV dysfunction.	IIB	C
Stage A*	In patients at high risk for developing HF, lipid disorders should be treated in accordance with contemporary guidelines.	I	A
	In patients at high risk for developing HF who have known atherosclerotic vascular disease, health care providers should follow current guidelines for secondary prevention.	I	C
Stage B†	Coronary revascularization should be recommended in appropriate patients without symptoms of HF in accordance with contemporary guidelines.	I	A
Stage C‡	Coronary revascularization is reasonable in patients with HF and normal LVEF and coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.	IIA	C
	Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use.	III	A
	Physicians should recommend coronary revascularization according to recommended guidelines in patients who have both HF and angina	I	A
HF with concomitant disorders	Physicians should prescribe antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease.	I	B
	Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina.	I	C

ACC = American College of Cardiology; AHA = American Heart Association; CAD = coronary artery disease; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction.[7]

*Patients at high risk for developing heart failure.

†Patients with cardiac structural abnormalities or remodeling who have not developed heart failure symptoms.

‡Patients with current or prior symptoms of HF.

with chronic heart failure.[16,17] Thus, a component of the observed benefit of these life-prolonging agents may be anti-ischemic, in addition to their more recognized role in myocardial remodeling. This commentary will focus on the debated role of 3 specific interventions targeting stable coronary artery disease in heart failure: lipid-lowering therapies, antiplatelet agents, and revascularization.

LIPID-LOWERING THERAPY

In national inpatient heart failure registries, rates of use of statins are approximately 40%, regardless of ejection fraction.[4] Lipid-lowering therapy does appear to be of value in preventing or prolonging onset of heart failure in high-risk patients.[18] Consistently, statins appeared to be of benefit among heart failure patients in observational studies.[19] On the other hand, in patients with chronic heart failure and reduced ejection fraction, 2 large clinical trials evaluating statin therapy failed to meet primary end points and did not appear to reduce all-cause mortality in patients with heart failure and coronary artery disease.[20,21] However, a recent meta-analysis of available data suggests that statins may reduce the burden of heart failure hospitalizations and contribute to relative improvement in ventricular function.[22] The Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) trial further demonstrated a reduction in fatal or nonfatal myocardial infarctions/strokes in heart failure patients treated with rosuvastatin.[20] Post hoc analyses of these trials suggest that certain biomarkers reflecting underlying inflammatory or profibrotic state may predict

favorable statin response, but these studies remain hypothesis generating.[23,24]

ANTIPLATELET AGENTS

Rates of utilization of aspirin at the time of admission for heart failure are roughly 40% in unselected heart failure populations.[4] Previous concerns about the concomitant use of aspirin with ACE inhibitors, due to a prostaglandin-mediated interaction,[25] were mitigated in a subsequent meta-analysis of 4 clinical trials that confirmed mortality benefit of ACE inhibition, regardless of aspirin administration.[26] The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial detected no differences in outcomes among patients randomized to aspirin, clopidogrel, or warfarin.[27] In fact, a slight increased heart failure hospitalization risk was observed in these trials in the aspirin arm.[27,28] It is, at present, unclear whether heart failure patients with comorbid coronary artery disease would benefit from antiplatelet therapies.[29]

REVASCULARIZATION

Although prompt revascularization after myocardial infarction reduces risk of incident heart failure,[30] coronary revascularization has not been shown to benefit heart failure patients definitively.[14,31] While it failed to meet its primary end point of a reduction in all-cause death, closer examination of the Surgical Treatment for Ischemic Heart Failure (STICH) trial reveals a 5% absolute reduction in cardiovascular death and a 10% absolute reduction in composite all-cause mortality and hospitalization with bypass surgery over optimal medical therapy at 56-month median follow-up.[31] In addition, roughly 13% of patients in STICH crossed over between treatment arms, and subsequent analyses of per-protocol and crossover STICH patient populations suggested a mortality benefit favoring coronary artery bypass grafting.[32] A time-varying analysis highlighted late benefit of coronary revascularization, partially balanced by an early hazard of adverse events.[31] Viability assessment[14] and stress testing to uncover inducible ischemia,[15] however, did not appear to identify individuals more likely to benefit from revascularization.

IS CORONARY ARTERY DISEASE A TARGET FOR THERAPY IN HEART FAILURE?

Coronary artery disease in heart failure represents a challenging substrate for targeted interventions. Adverse remodeling and scar formation from long-term ischemic damage may not be amenable to traditional coronary artery disease management. Similar to other chronic conditions such as chronic kidney disease, there may be a disconnect between traditional markers and risk factors of cardiovascular disease and outcomes in heart failure. This lack of association may pose distinct challenges to drug development, optimal dose finding, and drug monitoring. Furthermore, markers useful in predicting incident heart failure may be distinct from those that inform clinical worsening in existing heart failure. Thus, the efficacy of these interventions may depend on timing of initiation and individual patient risk profiles. Additionally, heart failure patients may be subject to strong competing risks, including worsening heart failure and sudden cardiac death. Interventions focused on reducing burden of coronary artery disease may not show benefit within the limited lifespan of an elderly heart failure patient. In fact, rates of clinically apparent ischemic events in the postdischarge period in patients hospitalized for heart failure are remarkably low,[33] despite nontrivial cardiac enzyme release in this population.[34]

Despite neutral primary results from studies examining coronary artery disease interventions in heart failure, certain patient-centered outcomes such as hospitalizations are reduced by lipid-lowering therapy and revascularization. More nuanced approaches for patient selection that diverge from traditional coronary artery disease risk paradigms may be required, including use of biomarker profiles. Important considerations in the decision-making calculus to prescribe or to withhold therapies include time course of benefit, cost-effectiveness, and patient preference. For now, with clinical equipoise, it may be prudent for clinicians to follow general ACC/AHA coronary artery disease guidelines for the treatment of this high-risk heart failure population.[35] Antiplatelet therapy and statins should remain a part of comprehensive heart failure management in many patients with heart failure and coronary artery disease, given that they are relatively inexpensive, well tolerated, and widely available. In the absence of definitive evidence, decisions about revascularization in heart failure should be individualized. Clinicians may consider omitting coronary artery disease interventions in select heart failure patients at high short-term risk of progressive heart failure by clinical estimates, those undergoing heart transplant/ventricular assist device placement evaluation, and patients pursuing palliative care options.

Future clinical trials should evaluate these interventions in important heart failure and coronary artery disease subsets to better determine which patient populations derive the greatest benefit. Ischemic cardiomyopathy has been the focus of novel treatment strategies including stem cell-based therapies. Stem cells may be particularly beneficial in this cardiac substrate given their neovascular growth effects in addition to their regenerative capacity.[36] We are currently awaiting more definitive clinical trial data evaluating stem cells in heart failure and coronary artery disease. Testing coronary artery disease therapies in earlier-stage heart failure populations with less myocardial scar may select patients more likely to benefit. Further data are required to determine whether aggressive coronary artery disease management in contemporary heart failure patients truly alters disease course and progression.

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