Cachexia: Common, Deadly, With an Urgent Need for Precise Definition and New Therapies

Mitja Lainscak, MD, PhD,a,b,* Gerasimos S. Filippatos, MD,c Mihai Gheorghiade, MD,d Gregg C. Fonarow, MD,e and Stefan D. Anker, MD, PhDa,f

Cachexia—sometimes also referred to as wasting disease, malnutrition, or hypercatabolism—has been described for centuries and has always raised ominous thoughts that “the end is near.” The disease is encountered in many malignant and nonmalignant chronic, ultimately fatal, illnesses. Yet, although cachexia is a deadly syndrome, little is known about its pathophysiology, and the debate regarding its definition is ongoing. Thus, the data on epidemiology can be contested, but a few things are certain: Cachexia is associated with exceedingly high mortality once the syndrome has fully developed, irrespective of the definition we apply, and it is associated with weakness, weight loss, muscle wasting, and inflammation. It is not simply an ancillary event, and it may contribute to the death of the patient either through effects on neuroendocrine and immune defense mechanisms or through protein calorie malnutrition. The therapeutic standard of care for cachexia remains undefined to date, with a few exceptions. Among the recognized approaches, exogenous oral amino acid supplementation appears very promising. Further research efforts are needed and they are ongoing. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:8E–10E)
fusion is caused by lack of agreement on the terms used to describe wasting. The scientific community frequently (mis)uses the terms “cachexia,” “anorexia,” “sarcopenia,” “malnutrition,” and even “hypercatabolism” as synonyms. Sar
copenia (aging-associated “normal” muscle wasting),16 for instance, may not be associated with significant weight change because the loss of muscle mass is counterbalanced by gains in fatty tissue. In anorexia (the term describes the loss of appetite, ie, a symptom), the bulk of the weight loss may be owing to consumption of fat for energy yield rather than muscle tissue loss. The term malnutrition is even more problematic because it is often used when cachexia is meant. Malnutrition suggests that the disease is associated with nutritional problems or failure, and it implies that it can be cured by adequate nutrition. It is a characteristic of cachexia that it cannot be cured by nutrition alone.17 The term hypercatabolism, finally, is difficult for a practicing clinician to apply for 2 reasons. First, it generally non-
identifiable by clinical examination. Second, it neglects the other side of the equation in cachexia pathophysiology, namely lack of anabolism, which itself recently was shown to be related to poor outcomes in CHF18 and is a key component of catabolic/anabolic imbalance in HF, which seems to be a key issue for the development of body wasting in cardiovascular illness.19,20

We are proponents of a clinical definition of cachexia that can be implemented in clinical practice to readily identify patients with this syndrome. The definition thus should not rely on the use of complicated tests or devices. Yet, it should be evidence based and the criteria should be validated as having prognostic significance. Indeed, the documentation of nonedematous weight loss of >6% of total body weight over a period of ≥6 months was the best predictor of mortality in a large cohort of patients with HF12; this study supports 2 core issues of cachexia: the weight loss itself, and, even more important, the dynamics of weight change. The latter was frequently neglected in earlier studies, leading to underestimation of cachexia prevalence and severity.1,3,4 However, besides weight changes, low body mass index can predict poor outcome in patients after myocardial infarction21 or in acute HF as well as in CHF.22 An interesting approach for cancer cachexia was recently reported. Fearon and colleagues23 evaluated a 3-factor profile of weight loss (≥10%), low food intake (≤1500 kcal/day [1 kcal = 4.2 kJ]), and systemic inflammation (C-reactive protein ≥10 mg/dL), and showed a better prognostic yield than for weight loss alone. These findings, which are in accordance with a previous report using a score of clinical and laboratory parameters in patients with HF,24 probably set the stage for an agreement on the basic criteria for a global cachexia definition. Efforts to reach a consensus on the definition of cachexia are underway (see www.cachexia.org).

Cachexia in cardiovascular illness unfortunately remains without specific treatment. Once the global definition for cachexia (ie, wasting disease) in cardiovascular illness and beyond is adopted, intensified therapeutic efforts will be urgently needed. We hope that future therapies will be able to stop or even reverse the deadly cascade of events leading to full-blown cachexia and improve the quality of life and clinical outcomes for our patients. Currently, no approved therapies for cachexia exist, apart from growth hormone and some appetite stimulants in acquired immunodeficiency syndrome–induced cachexia. Nonetheless, causative ther-

apy is still not available, although some potential candidates have been tested.20,25,26 Among them, exogenous oral amino acid (AA) supplementation appears very promising. AAs stimulate muscular protein synthesis and mitochondrial biogenesis and improve energy performance in wasting syndromes. Intriguing clinical and basic science results are summarized elsewhere in this supplement. We hope to stimulate new developments in the field, including evidence-

based treatments for cachexia. Great efforts in basic and clinical science are underway, and the results are eagerly awaited.

Author Disclosures

The authors who contributed to this article have disclosed the following industry relationships:

Mitja Lainscak, MD, PhD, has no financial arrange-
ment or affiliation with a corporate organization or a man-
ufacturer of a product discussed in this supplement.

Gerasimos S. Filippatos, MD, has received research/
grant support from GlaxoSmithKline, Medtronic, Inc., Ot-
suka Pharmaceutical Co., and Vifor International Inc.

Mihai Gheorghiade, MD, serves as a consultant to Debbio Pharm, ErreKappa Euroterapici, GlaxoSmithKline, Medtronic, Inc., and PDL BioPharma; has received re-
search/grant support from Merck & Co., Inc., the National Institutes of Health (NIH), Otsuka Pharmaceutical Co., SCIOS Inc., and Sigma-Tau Pharmaceuticals; and has received honoraria from Abbott Laboratories, AstraZeneca Pharmaceuticals, GlaxoSmithKline, Medtronic, Inc., Otsuka Pharmaceutical Co., PDL BioPharma, SCIOS Inc., and Sigma-Tau Pharmaceuticals.

Gregg C. Fonarow, MD, has worked as a consultant for Amgen Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Inc., Merck & Co., Inc., NitroMed, Inc., Otsuka Pharmaceutical Co., Pfizer Inc, sanofi-aventis, Schering-Plough, and Scios, Inc.; has re-
ceived research/grant support from Amgen Inc., Glaxo-
SmithKline, Medtronic, Inc., and PDL BioPharma, the National Institutes of Health (NIH), Pfizer Inc, and Scios, Inc.; and has received honoraria from Abbott Laboratories, Amgen Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, King, Inc., Merck & Co., Inc., NitroMed, Inc., Pfizer Inc, sanofi-aventis, Schering-Plough, and Scios, Inc. and Stefan D. Anker, MD, PhD, has worked as a consultant for Amgen Inc., Biomeasure Inc., Brahms Diagnostica, and Vifor International Inc.; has received research/grant support
from Amgen Inc., Brahms Diagnostica, Vasogen Inc., and Vifor International Inc.; and has received honoraria from Amgen Inc., Berlin-Chemie, Brahms Diagnostica, Merck & Co., Inc., Otsuka, sanofi-aventis, Vasogen Inc., and Vifor International Inc.