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Permalink

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Journal

Journal of the American College of Cardiology, 43(8)

ISSN

0735-1097

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Publication Date

2004-04-01

DOI

10.1016/j.jacc.2003.11.039

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Peer reviewed

Reverse Epidemiology of Conventional Cardiovascular Risk Factors in Patients With Chronic Heart Failure

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Traditional risk factors of a poor clinical outcome and mortality in the general population, including body mass index (BMI), serum cholesterol, and blood pressure (BP), are also found to relate to outcome in patients with chronic heart failure (CHF), but in an opposite direction. Obesity, hypercholesterolemia, and high values of BP have been demonstrated to be associated with greater survival among CHF patients. These findings are in contrast to the well-known associations of over-nutrition, hypercholesterolemia, and hypertension with a poor outcome in the general population. The association between traditional cardiovascular risk factors and an adverse clinical outcome in CHF patients is referred to as “reverse epidemiology.” The mechanisms for this inverse association in CHF is not clear. There are other populations with a similar risk factor reversal phenomenon, including patients with end-stage renal disease receiving dialysis, those with advanced malignancies, and individuals with advanced age. Several possible causes are hypothesized: the time discrepancy of the competing risk factors may play a role; the presence of the “malnutrition-inflammation complex syndrome” in CHF patients may explain the existence of reverse epidemiology; and a decreased level of lipoprotein molecules may distort their endotoxin-scavenging role, predisposing CHF patients with a low serum cholesterol level to inflammatory consequences of endotoxemia. It is possible that new goals for such traditional risk factors as BMI, serum cholesterol, and BP should be developed for CHF. Reverse epidemiology of conventional cardiovascular risk factors is observed in CHF and may have a bearing on the management of these patients; thus, it deserves further investigation. (J Am Coll Cardiol 2004;43:1439–44) © 2004 by the American College of Cardiology Foundation

Chronic heart failure (CHF) is a progressive disease that results in substantial morbidity and mortality (1,2). The conventional cardiovascular risk factors (i.e., obesity, hypercholesterolemia, hypertension) are associated with an independently increased risk of developing CHF and mortality in the general population (3). Numerous recent reports indicate that in marked contrast to the general population, where these cardiovascular risk factors are associated with increased risk of an adverse outcome, a higher body mass index (BMI), increased serum cholesterol concentration, and higher blood pressure (BP) values are strongly correlated with decreased morbidity and mortality in CHF patients (Table 1) (4–6). These paradoxical observations, which have also been reported in patients with end-stage renal disease (ESRD) undergoing dialysis treatment, have been referred to as “reverse epidemiology” (7). These studies call into question the practice of extrapolating cardiovascular risk factor targets or goals derived from the general popu-

lation to the CHF population without separate study. The phenomenon of an established risk factor in the general population having a markedly different and indeed opposite predictive pattern may not be unique to the CHF or ESRD populations. Elderly individuals in nursing homes (8), hospitalized patients (9), patients with malignancy (10), and possibly other subpopulations may have similar reverse epidemiology. Hence, a better understanding of the causes of reverse epidemiology in CHF may help refine the treatment goals and result in an improved outcome in this and other similar but distinct populations.

Weight and BMI: is obesity favorable? Epidemiologic studies have shown a strong relationship between obesity and increased risk of cardiovascular disease and mortality in the general population (11–13). In some studies of normal adults, a “J” or “U” curve effect has been observed, in which those individuals with a low BMI also demonstrated increased mortality, although not as high as that in obese individuals (12,13).

Increased BMI is associated with an increased risk of heart failure (3,14). However, patients with more severe CHF tend to have lower BMI values than do age- and gender-matched control subjects from the general population (15–17). A study of prognostic variables in 401 patients with CHF did not find overweight status to be a risk factor

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Manuscript received September 7, 2003; revised manuscript received October 30, 2003, accepted November 4, 2003.

Abbreviations and Acronyms

- BMI = body mass index
- BP = blood pressure
- CHF = chronic heart failure
- ESRD = end-stage renal disease
- MICS = malnutrition-inflammation complex syndrome
- NYHA = New York Heart Association
- PEM = protein-energy malnutrition
- TNF = tumor necrosis factor

for mortality, despite inclusion of >40% overweight patients with BMI >26 kg/m² (18). In the Systolic Hypertension in the Elderly Program study, overweight status was associated with a decreased stroke risk and reduced total mortality, as compared with lean subjects with CHF (19). Horwich et al. (5) studied 1,203 individuals with moderate to severe CHF (>60% in New York Heart Association [NYHA] functional class IV). A higher BMI was associated with a better two-year survival rate. One- and five-year survival showed the same trend, although the association was not statistically significant. Multivariate analysis showed an inverse association between BMI and mortality (Fig. 1).

In the Rotterdam Study cohort (20), both cardiac death and all-cause mortality were lower in obese CHF patients. Davos et al. (21) examined the impact of BMI in 589 patients with CHF who did not have cachexia. On multivariate analyses, a higher BMI (as a continuous variable) conferred better survival (21). Lissin et al. (22) reported a similar finding in 522 veteran patients with CHF, in that patients with BMI <22 kg/m² had worse survival and those with BMI >30 kg/m² had the best survival. Finally, Lavie et al. (23) also reported the obesity paradox, in that a better event-free survival was observed with higher body-composition quintiles in 209 consecutive ambulatory patients with NYHA functional class I to III heart failure. In this study, the BMI and percent body fat associated with an adverse outcome were at levels generally considered to be “healthy,” and not at levels consistent with a cachectic state (23). It should be noted that this so-called “obesity paradox” is not restricted to CHF but is indeed a well-described

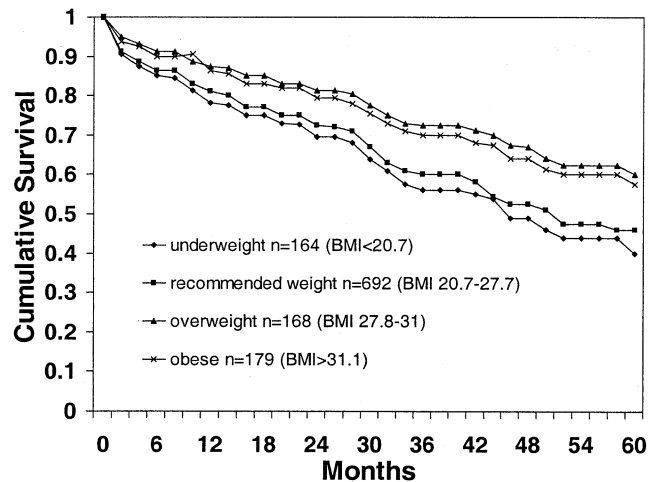


Figure 1. Risk-adjusted survival curves for the four body mass index (BMI) categories at five years. Survival was significantly better for the overweight and obese BMI categories. (From Horwich et al. [5], with permission.)

phenomenon in several other distinct populations, including ESRD patients undergoing dialysis (7,24) and elderly individuals (8).

Serum cholesterol: is hypercholesterolemia desirable?

Although hypercholesterolemia is a well-defined risk factor for morbidity and mortality in the general population (25), the relationship between cholesterol and clinical outcome in patients with CHF does not appear to be conventional. Vredevoe et al. (26) reported that low total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations related to impaired survival in 109 CHF patients. In another study by Richartz et al. (27), the perioperative mortality of 45 patients with severe CHF supported by a left ventricular assist device was significantly associated with hypocholesterolemia, whereas hypercholesterolemia was protective. Rauchhaus et al. (28) found that low total serum cholesterol levels (<200 mg/dl) were predictive of impaired 12-month event-free survival in 51 patients with CHF, independent of the cause of CHF (ischemic or nonischemic) and the presence of cachexia. The largest epidemiologic study in this regard was conducted by Horwich et al. (6), in that among

Table 1. Reverse Epidemiology of Cardiovascular Risk Factors in Chronic Heart Failure

| Risk Factors of Cardiovascular Disease | Direction of the Associations Between Risk Factors and Outcomes | | Comments |
|--|---|---|---|
| | General Population | CHF Patients | |
| BMI | High BMI and obesity are deleterious (13). | High BMI and obesity are protective (5,19-23,37). | Increased BMI is a risk factor for CHF development (3,14). Elderly, smoking, maintenance dialysis, and hospitalized patients have an inverse association similar to CHF patients (7). |
| Serum cholesterol | Hypercholesterolemia, high LDL cholesterol, and low HDL cholesterol are deleterious (25). | Hypercholesterolemia (and maybe high LDL cholesterol) is protective (6,22,26-28). | There may be similar associations between low cholesterol and mortality in elderly or smoking persons and dialysis or AIDS patients (7,29,30,36). |
| BP | Hypertension is deleterious (37). | A low systolic BP often indicates poor outcome (1,20,38-41). | Similar reverse associations between BP and outcome have been described in dialysis patients (43). |

BMI = body mass index; BP = blood pressure; CHF = chronic heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

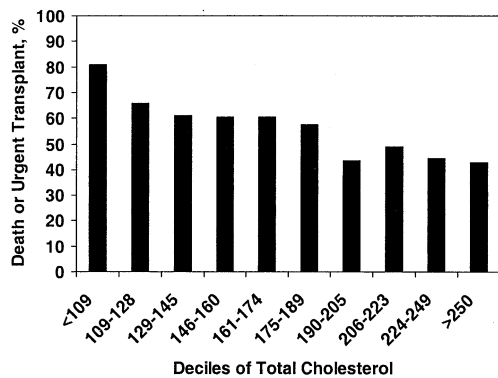


Figure 2. Five-year rates of death or urgent heart transplantation by deciles of total cholesterol. (From Horwich et al. [5], with permission.)

1,134 patients with advanced CHF, those with a low total cholesterol level had a significantly lower albumin level, left ventricular ejection fraction, and cardiac output. Total, low-density lipoprotein, and high-density lipoprotein cholesterol and triglycerides each predicted survival significantly ($p \leq 0.01$) on univariate analysis, with improved survival at higher levels (Fig. 2). After adjustment for risk factors using a Cox proportional hazards models, relative risks were 2.07, 1.37, 1.39, and 1.01 for the first, second, third, and fourth total cholesterol quintiles, respectively, as compared with the fifth (highest) quintile (6). The cohort study by Lissin et al. (22) showed that surviving patients with CHF had a higher prevalence of hyperlipidemia than did deceased patients.

Similar findings regarding the association of low serum cholesterol and poor outcome have been reported for elderly individuals (29-32). Volpato et al. (30,31) found that among 4,128 elderly patients with a mean age of 79 years, the all-cause mortality was significantly higher in those with a low serum cholesterol level, defined as ≤ 160 mg/dl, as compared with those with normal or high serum cholesterol concentrations. Similar to patients with CHF, hypocholesterolemia has been shown to be associated with adverse outcomes in ESRD patients undergoing dialysis (33), cancer patients (34), and individuals with AIDS (35).

Blood pressure: are lower blood pressure values deleterious? The role of hypertension as a risk factor for increased cardiovascular or cerebrovascular events in the general population is indisputable (36). However, elevated BP may not represent the primary risk for overall survival in CHF patients; several studies have failed to show that high BP is an independent mortality risk factor in CHF patients (20,37-39). Ghali et al. (37) showed that in 78 patients with decompensated CHF, both systolic and diastolic BP levels were lower in the deceased patients compared with survivors. In another cohort of 102 patients with CHF who underwent echocardiography, Rihal et al. (38) showed that higher systolic BP was independently predictive of subsequent survival. Cowie et al. (39) demonstrated that in 220 patients with incident CHF, higher systolic BP was independently predictive of improved cardiovascular survival.

Similarly, in the Rotterdam Study, a higher BP level conferred a more favorable prognosis among 181 subjects with CHF (20). In a large cohort of outpatients consecutively enrolled in the Registry of Italian Network on CHF (1), higher systolic BP was among very few independent predictors of survival in 1,033 elderly patients (age >70 years) with CHF. In the study by Muntwyler et al. (40) of 411 CHF patients (NYHA functional class II to IV), one of the statistically significant ($p < 0.05$) predictors of mortality was lower systolic BP (relative risk 2.4). Recently, Poole-Wilson et al. (41) conducted a randomized, double-blinded study of 3,164 patients with CHF and showed that higher systolic BP at baseline was independently associated with a statistically significant lower mortality rate. Similar to patients with CHF, in dialysis-maintained patients, a reverse association has been reported between BP and mortality (42).

Possible explanations for reverse epidemiology. The concept of reverse epidemiology appears at first to be mystifying, especially because obesity, increased levels of serum cholesterol, and high BP values are such well-established risk factors for ischemic heart disease and CHF in the general population. The paradox becomes even more paramount when it is recognized that it is not a question of the existence or lack of an association between these risk factors and clinical outcomes, but often the complete reversal and indeed the opposite direction of this relationship. Hence, there must be prevailing conditions that are characteristically present in CHF patients, which render them more susceptible to a poor outcome when low body mass, low BP, or decreased serum values of serum cholesterol are present. Alternately, once CHF develops, these factors may actually provide patients with protection against CHF disease progression. Several suggested explanations are offered as possible mechanisms for this inverse association.

Time discrepancies among competitive risk factors. Survival advantages that exist in obese and hypercholesterolemic CHF patients with high BP values may, in the short term, outweigh the harmful effects of these risk factors on cardiovascular disease in the long term. Because CHF patients have a mortality risk that is substantially greater than that in the general population (1), the long-term effects of these risk factors on future mortality may be overwhelmed by the short-term effects of other factors on CHF mortality. In the U.S. general population, as well as in most industrialized countries, manifestations of over-nutrition, such as obesity and hypercholesterolemia, are major risk factors for cardiovascular mortality (25,43). These are also countries where people have a greater life expectancy, as compared with individuals in other parts of the world. In contrast, in developing countries, undernutrition is still a powerful determinant of a poor clinical outcome and morbidity and mortality, leading to a shorter life expectancy (44). Thus, in CHF patients who have a short life expectancy, any factor that may improve short-term survival, such

as obesity or hypercholesterolemia, may exert a desirable effect on longevity, whereas conditions that are traditionally associated with long-term survival may not be relevant.

Malnutrition-inflammation complex syndrome (MICS). Cardiac cachexia has been identified as an independent risk factor for mortality in CHF (17). Twenty-four percent of CHF patients have hypoalbuminemia (<3.5 mg/dl) and 68% have muscle atrophy (15). In advanced CHF, cachexia and wasting appear to be independent predictors of increased mortality (45). An important feature of cardiac cachexia is related to the inflammatory syndrome (16). Tumor necrosis factor (TNF)-alpha has been reported to be significantly increased in patients with CHF cachexia (46), as in the cases of cachectic patients with a variety of cancers, infections, or vascular diseases (47). Anker et al. (48) found that TNF-alpha was twofold higher in cachectic CHF patients than in non-cachectic control subjects. This chronic inflammatory state may have resulted from bacterial or endotoxin translocation due to bowel wall edema after severe heart failure (49). The inflammatory response may be responsible for the wasting syndrome and hypoalbuminemia in CHF (50). It has been postulated that the common link between CHF and cachexia is inflammation (51). The mechanism for the development of protein-energy malnutrition (PEM) in CHF patients may be cytokine activation associated with increased endotoxin absorption or reduced clearance, especially in the setting of hypolipoproteinemia. On the other hand, PEM and inflammation may each independently contribute to hypoalbuminemia, cachexia, and subsequently increased morbidity and mortality in CHF. However, as both PEM and inflammation are strongly associated with each other and can change many nutritional measures in the same direction, and because the relative contributions of measures of these two conditions to each other and to outcomes in CHF patients are not yet well defined, we propose to use the term MICS, which has also been suggested for a similar condition in dialysis patients (52).

The existence of paradoxical risk factors could be accentuated by MICS, possibly in several ways. First, patients who are underweight or who have low serum cholesterol may be suffering from MICS and its poor outcome (51). Second, the aforementioned paradoxical factors may indicate a state of undernutrition, which may predispose to infection or other inflammatory processes (53). Finally, when individuals are malnourished, they are more susceptible to the ravages of inflammatory diseases (54). Hence, any condition that potentially attenuates the magnitude of PEM or inflammation should be favorable to CHF patients. A significant association between low diastolic BP, low BMI, and risk of death in a cohort of CHF patients has been shown (22). In dialysis patients, the association between low BP and an adverse outcome may also reflect a greater systemic inflammatory response in such patients (54). Hence, the association between lower BP and a worse

outcome may account for the lower BP association with MICS in CHF patients.

Endotoxin-lipoprotein hypothesis. Lower serum total cholesterol and lipoprotein concentrations are strongly and independently associated with impaired survival in CHF patients (55). Increases in lipopolysaccharide levels have been shown in CHF patients as compared with the general population (53,55). Higher concentrations of total cholesterol may reflect a richer pool of internal lipoproteins that can actively bind to and remove circulating endotoxins, thus removing their deleterious effect in causing inflammation and subsequent atherosclerosis in CHF patients (53). Plasma concentrations of lipopolysaccharides are raised in edematous patients with CHF who also show substantial immune activation and inflammation (53). The finding of higher lipopolysaccharide concentrations in patients with severe CHF (53), as well as abnormal monocyte responsiveness to lipopolysaccharides (56), makes it a strong possibility that mononuclear cells contribute to the generation of inflammatory cytokines in CHF. Rauchhaus et al. (28,55) have hypothesized that there is an optimal lipoprotein concentration below which a lipid reduction would be detrimental due to inadequate lipopolysaccharide binding.

Survival bias. Because CHF patients have undergone specific processes of selection and survival, their characteristics may not be similar to those of the general population. According to an analysis based on the National Health and Nutrition Examination Survey (57), in the U.S., there are over 50 million patients with cardiac or vascular disease who are at increased risk of developing CHF. However, the number of people with clinically evident CHF is approximately five million. A higher proportion of patients with heart disease and conventional risk factors do not reach the CHF stage due to their higher mortality, as compared with those with heart disease lacking these risk factors. Hence, those who manage to survive to reach CHF despite conventional risk factors may have other protective factors that otherwise negate the adverse effects of the conventional risk factors. Whatever the survival features are, these "unfortunately lucky" individuals may be considered as "specifically selected" patients who are not necessarily genetically or phenotypically similar to their predecessors and may not have the survival characteristics and epidemiologic features of their progenitors. Hence, a survival bias, which is a form of selection bias, may heavily influence the epidemiologic constellations in this smaller proportion of cardiovascular survivors (i.e., CHF patients).

Reverse causation. The direction of a causal pathway may be reversed in the paradoxical associations described in CHF patients. Hence, it may not be normotension or hypotension, per se, that is detrimental, but rather the underlying cause of low BP (i.e., cardiac pump failure). This phenomenon, known as "reverse causation" (58), indicates that low BP, BMI, or serum cholesterol values are not etiologically linked to a higher mortality rate in CHF patients; they are merely markers of a poor outcome.

However, even if these associations are devoid of causation or have a reversed direction, the counterfactual inference implies that maneuvers that would avoid hypotension or weight loss in CHF patients may be beneficial in their survival.

Clinical implications. Why were these striking findings regarding an inverse association between conventional cardiovascular risk factors and mortality in CHF only recently reported, and should they be believed? A publication bias may have handicapped or delayed reporting such paradoxical findings in CHF patients, as the investigators' first impression upon encountering results with an inverted association may be to consider them erroneous (59). As more reports indicative of reverse epidemiology in CHF have been published recently, more investigators appear to have been encouraged to report their "reverse" findings. The concept of CHF being a systemic inflammatory disease is relatively recent and may have provided biologic plausibility to the seemingly paradoxical associations.

Although the term "reverse epidemiology" may be a misnomer, we advocate the use of this nomenclature, not only because it is stimulating but also because this phenomenon has been clearly described in dialysis patients under the same terminology. The etiology of reverse epidemiology in CHF patients may be quite different for various risk factors. In other words, factors that lead to a positive association between obesity and better survival in these patients may be different from those leading to the association between lower BP and mortality. Nevertheless, it is important to first exhaust the possibility of one single unifying entity to account for all or most of the aforementioned risk factor reversals. We believe that MICS is the best candidate. Nevertheless, we have offered several additional plausible hypotheses.

We believe that in CHF patients, more attention should be focused on optimal management of undernutrition and inflammation, based on possible mechanisms responsible for the reverse epidemiology. However, premature conclusions to lower doses or discontinue antihypertensive or anti-hyperlipidemic treatment should be avoided until such information is forthcoming. The antihypertensive drugs, neurohormonal antagonists, angiotensin-converting enzyme inhibitors, and beta-blockers clearly prolong life in CHF patients, irrespective of their hemodynamic effects and the existence of reverse epidemiology for BP and outcome. The antihypercholesterolemic agent, hydroxymethylglutaryl coenzyme A reductase inhibitor (a statin), may have an anti-inflammatory effect that can be beneficial in the management of the elements of MICS and improved outcome in CHF patients, irrespective of cholesterol-lowering effects (60). A recent study by Horwich et al. (61) has shown an independent association of statin use and lower mortality in patients with ischemic and nonischemic heart failure.

Although the data presented in this review suggest that a higher BMI, higher BP, and hypercholesterolemia are associated with reduced morbidity and mortality in the

vulnerable population with CHF, it is possible that, in the long run, CHF patients with these risk factors may suffer from more cardiovascular consequences if they survived for a sufficiently longer period of observation. As more effective treatments for CHF patients become available, it is possible that there may be a "reversal of the reverse epidemiology" and a return to traditional epidemiology for many subgroups of CHF patients, as currently found in heart transplant patients (62). The question may remain unanswered as to what is indeed the normal epidemiology and what is reverse. Identification of the mechanisms for the reversal of the traditional associations will be most beneficial to the improving our understanding of the pathophysiology of CHF and improving the care of these patients.

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