

How Deadly Is the “Deadly Quartet”?

A Post-CABG Evaluation

Dennis L. Sprecher, MD,* Gregory L. Pearce, MS

Cleveland, Ohio

OBJECTIVES	The aim of the study was to determine the value of a cluster of metabolic risk factors in predicting mortality after coronary artery bypass surgery (CABG).
BACKGROUND	The “deadly quartet” of metabolic risk factors (i.e., obesity, diabetes, hypertension, and hypertriglyceridemia) has been associated with coronary heart disease in healthy population studies. The expected influence of the cluster on survival in secondary prevention remains untested overall as well as by gender.
METHODS	Patients with lipid profiles undergoing primary isolated CABG (n = 6,428) between 1987 and 1992 were followed a median of eight years. Cox models were used to evaluate all-cause mortality. Metabolic risk factors were incorporated as the sum of deadly quartet risk factors present in each patient (0 to 4). The role of gender as it relates to survival and metabolic risk clusters was also examined.
RESULTS	The sum of deadly quartet risk factors showed a significant relationship to mortality as the hazard ratio increased from 1.64 (confidence interval [CI] = 1.34–2.01) for one risk factor to 3.95 (2.73–5.69) for four risk factors. Annualized mortality ranged from 1% per year in patients with no risk factors to 3.3% per year in patients with all four risk factors. Within gender, the hazard ratio associated with four risk factors was 2.58 for men and 13.39 for women. The expected clustering of risk factors was 8% compared to the observed clustering of 10% in men and 21% in women.
CONCLUSIONS	This cohort showed risk factor clustering beyond that expected due to chance, particularly in women. Even after revascularization, survival is diminished for patients with members of a family of metabolic risk factors at the time of surgery. (J Am Coll Cardiol 2000;36:1159–65) © 2000 by the American College of Cardiology

The “deadly quartet” (obesity, diabetes mellitus, hypertension, and hypertriglyceridemia) was characterized by Kaplan (1) with inspiration from Reaven (2), who defined the metabolic syndrome. This grouping of known metabolic risk factors is highly associated with coronary heart disease (CHD) (3,4), and typically viewed as associated with insulin resistance (5). The increase in risk for cardiovascular disease (CVD) as the number of risk factors progressively increases has been well documented (6). However, the demonstration of clustered risk in the primary prevention setting cannot necessarily be extrapolated to secondary prevention efforts. Although a recent analysis characterized risk clustering and 16-year outcomes in the follow-up of the healthy population of the Framingham cohort (7), both the degree of clustering and its impact on mortality have not been characterized in those with established coronary artery disease (3).

Separating the contributions of each of these factors to atherogenic risk has been complex. There is evidence that the members of the deadly quartet interact with one another as they relate to CHD (8–12), and even potentially represent a common metabolic abnormality (5). Defining the ultimate influence on mortality of some or all members of this metabolic quartet in patients with CHD could reshape current treatment strategies in secondary prevention (13–15). Such risk stratification could also be factored into

decisions related to the benefits associated with surgical revascularization procedures (i.e., coronary artery bypass surgery). For example, the presence of diabetes, one member of the quartet, has already been reported to lead to greater mortality and event rates after coronary artery bypass graft surgery (CABG) (16–18).

We examined the post-CABG registry at the Cleveland Clinic to determine whether the deadly quartet resulted in increased mortality over the average eight years of follow-up. Further, we explored the role of gender in the susceptibility to these clustered risk factors.

METHODS

Study population. Nine thousand five hundred and forty-four (9,544) patients had primary isolated CABG at the Cleveland Clinic between 1987 and 1992. Exclusions were made for hospital death (n = 210) and lack of complete lipid evaluations (total cholesterol, HDL-c [high density lipoprotein cholesterol] and triglycerides) performed prior to surgery (n = 2,906). The resultant study cohort numbered 6,428 patients. Low density lipoprotein cholesterol [LDL-c] was not considered, because of inability to accurately measure LDL-c when triglycerides exceed 400 mg/dl. Lipid measurements were drawn in the fasting state a median of five days before surgery (65% before surgical admission). The Cleveland Clinic Foundation laboratory was standardized by the Centers for Disease Control [Part III], with accreditation through the College of American

From the *Section of Preventive Cardiology, Department of Cardiology, The Cleveland Clinic Foundation, Cleveland, Ohio.

Manuscript received October 19, 1999; revised manuscript received March 24, 2000, accepted June 1, 2000.

Abbreviations and Acronyms

BMI	=	body mass index
CABG	=	coronary artery bypass graft
CHD	=	coronary heart disease
CI	=	confidence interval
CVD	=	cardiovascular disease
DM	=	diabetes mellitus
HDL-c	=	high density lipoprotein cholesterol
HR	=	hazard ratio
HRT	=	hormone replacement therapy
ITA	=	internal thoracic artery
LDL-c	=	low density lipoprotein cholesterol
TG	=	triglycerides

Pathology during the study period. Specifically trained personnel abstracted data from the medical record using a standardized data-collection form that required either numeric entries or checks (yes/no) for the risk factors of interest. The outcome for this study was all-cause mortality as obtained from either routine patient/family contact or the Social Security Administration mortality index. Median follow-up time for the 5,568 surviving patients was 8.2 years.

Statistical analyses. The deadly quartet risk factors are defined as history of diabetes mellitus (DM) based on known pharmacologic treatment of diabetes, hypertension established through repeated systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg or pharmacologic treatment of hypertension, body mass index (BMI) in the top quartile (>30.0) and triglyceride (TG) in the top quartile (>219 mg/dl). The upper quartiles were established within the study cohort because of concerns about extrapolating parameters from the primary prevention setting to secondary prevention. The upper TG quartile from this study corresponds approximately to the upper decile of similar-age subjects in the Framingham Study (19), and the Lipid Research Clinic Prevalence study (20). The sum of these risk factors is represented by integer values from zero to four.

The probability of having a given risk factor is characterized by the binomial distribution, and the incidence of having a given risk factor ranges from 0.20 for diabetes to 0.55 for hypertension in this population. The expected probability of having 0, 1, 2, 3 or 4 risk factors has been estimated based on a binomial expansion assuming independent risks. Expected distributions were based on combined data for men and women because we had no a priori expectations of gender differences (7). Cox proportional hazards modeling (PROC PHREG, SAS Institute, Cary, North Carolina) was used to assess the relative importance of baseline risk factors to the end points (21). Tied event data were handled using Efron's method of approximation (22). Overall model significance was assessed with likelihood-ratio tests, and significance of each variable in the model with the Wald test. Dummy variable coding was developed within the framework of Cox proportional haz-

ards modeling to compare patients with 1, 2, 3 and four of the deadly quartet components to patients with none of the components. Hazard ratios (HRs) are presented (with 95% confidence intervals [CIs]) to show the risk of an event when the factor is present. These risk estimates represent the average risk when 1, 2, 3, or 4 risk factors are present and do not speak to risk associated with a specific risk factor.

A three-step strategy was taken to evaluate the importance of the deadly quartet. First, unadjusted HRs were calculated followed by age-adjusted HRs. Finally, a model adjusting for age and surgical variables (left ventricular function, extent of disease, and internal thoracic artery [ITA] use) was developed. To determine whether the conclusions regarding risk progression hinged on a single member of the deadly quartet, four models were built sequentially, holding each individual risk factor to zero (not presented).

Information was not available regarding certain medications (e.g., hormone replacement therapy [HRT], lipid-lowering agents) that are known to impact TG values. Therefore, analyses were undertaken to determine the likelihood that conclusions relating the deadly quartet sum to mortality could be jeopardized by TG category misclassification. Progressive percentages of "presumed" misclassified patients were randomly identified and reallocated to the opposite TG group (e.g., high TG due to HRT reclassified as normal TG). Hazard ratios for the deadly quartet sum were recalculated to determine consistency with the reported relationship. Both a gender main effect and an interaction term between gender and the sum of deadly quartet risks were included in the fully adjusted model to examine the potential role of gender with regard to all-cause mortality. A statistically significant interaction term would lead to examination of models stratified by gender. Modeling included testing the assumption of proportional hazards.

RESULTS

Patient characteristics. Table 1 shows the presentation characteristics of this post-CABG population with regard to the relevant risk factors. The p values resulting from gender comparisons indicate that women typically show greater risk. Of patients undergoing primary isolated CABG during this time frame, 2,906 (31%) were missing either TG or HDL-c values before surgery. Cases missing lipids were more likely to be emergent and use saphenous vein grafts than were those with complete lipid profiles. The group with missing values also had more women, was older and had worse left ventricular function than did those with complete lipid profiles ($p = 0.001$ for all). Consequently, a worse survival outlook was seen in those patients without baseline lipid measurements.

All-cause mortality for the study population was 13% ($n = 860$). Women suffered a greater raw mortality rate than did men (17% vs. 12%), but this was not statistically significant after adjusting for age, surgical variables and the

Table 1. Presentation Characteristics of Primary Isolated CABG Patients Overall and by Gender

	Overall	Men	Women	P Value*
Number	6,428	5,175	1,253	
Age	62 ± 10	61 ± 10	65 ± 9	< 0.001
Hx of DM	1313 (20%)	917 (18%)	396 (32%)	< 0.001
Hx of HTN	3549 (55%)	2689 (52%)	860 (69%)	< 0.001
TG > 219 mg/dl	1607 (25%)	1230 (24%)	377 (30%)	< 0.001
BMI > 30	1679 (26%)	1261 (24%)	418 (33%)	< 0.001
Race				< 0.001
White	5833 (91%)	4660 (90%)	1173 (94%)	—
Black	109 (2%)	73 (1%)	36 (3%)	—
Other	486 (8%)	442 (9%)	44 (4%)	—
Smoking	3230 (50%)	2723 (53%)	507 (41%)	< 0.001
2- 3-Vessel DX†	6050 (94%)	5175 (95%)	1156 (92%)	0.002
Severe LVF‡	570 (9%)	466 (9%)	104 (8%)	0.43
ITA used	5528 (86%)	4606 (89%)	922 (74%)	< 0.001
Deadly quartet sum				
0	1599 (25%)	1425 (28%)	174 (14%)	< 0.001
1	2442 (38%)	2011 (39%)	431 (34%)	0.003
2	1597 (25%)	1218 (24%)	379 (30%)	< 0.001
3	648 (10%)	434 (8%)	214 (17%)	< 0.001
4	142 (2%)	87 (2%)	55 (4%)	< 0.001

*p Values resultant from male versus female comparison. †Two- or three-vessel coronary artery disease (stenosis >50%). ‡Severe left ventricular dysfunction (ejection fraction <20%).
 HTN = hypertension.

identified metabolic risk factors (HR = 0.95, CI = 0.81 to 1.12, p = 0.55). The mortality rate increased as the number of deadly quartet risk factors increased in all cases (Fig. 1, p < 0.001 for all).

Expected risk factor distributions and observed distributions are shown in Figure 2. An enhanced frequency of observed versus expected distributions was noted for those with zero risk factors and those with three or four risk factors.

Deadly quartet effect. We first examined the univariate risk associated with the sum of the four deadly quartet components (e.g., a patient with DM and TG = 230 mg/dl would have two of the four). After the univariate look, age-adjusted models were built followed by age- and surgical variable-adjusted models. Adjustments for smoking

status and race did not affect the results materially (data not shown). Table 2 shows that the hazard associated with the deadly quartet increased from 1.64 to 3.95 as the risk factors accumulated whether adjusted or not. The proportional hazards assumption was not perfectly met. Therefore, the estimated HRs for the number of deadly quartet risk factors are conservative as they represent an average hazard over the course of the study.

Based on the analyses involving TG misclassification, at least 60% of patients would have to have misclassified TGs to significantly impact the observed relationship between the deadly quartet sum and mortality. A piecewise exponential model accounting for variable hazards across time corroborated the results of the Cox models (data not

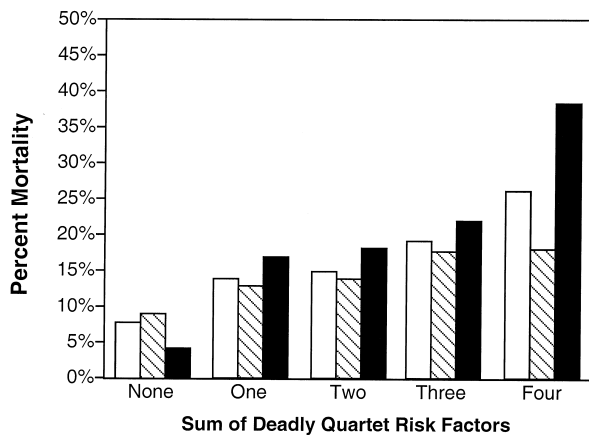


Figure 1. Raw incidence of mortality overall and by gender. Open bars = overall risk factors; hatched bars = male risk factors; solid bars = female risk factors.

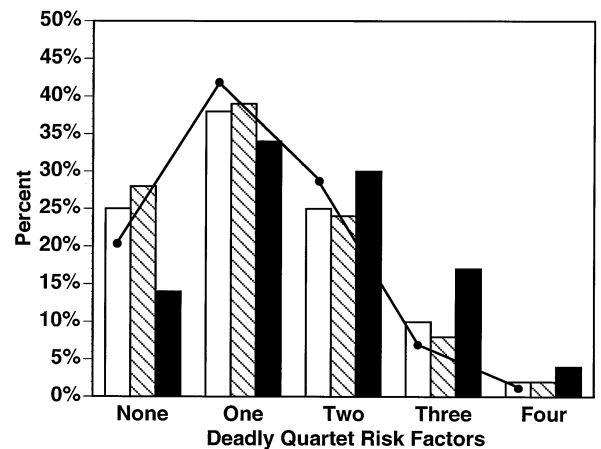


Figure 2. Expected (line) and observed (bars) prevalence of patients with zero, one, two, three or four of the deadly quartet risk factors (hypertension, diabetes, hypertriglyceridemia, obesity). Open bars = overall risk factors; hatched bars = male risk factors; solid bars = female risk factors.

Table 2. Deadly Quartet Hazard Ratio (HR) Estimating the Risk of Mortality with 95% Confidence Intervals (95% CI) Estimated from Cox Proportional Hazards Models Unadjusted, Age-Adjusted and Age- and Surgical Variable-Adjusted*

Quartet	Unadjusted		Age Adjusted		Age + Surgical Adjusted	
	HR	95% CI	HR	95% CI	HR	95% CI
0 of 4	1.00	—	1.00	—	1.00	—
1 of 4	1.73	1.42-2.12	1.62	1.32-1.99	1.64	1.34-2.01
2 of 4	1.94	1.57-2.40	1.94	1.57-2.40	1.95	1.57-2.41
3 of 4	2.52	1.97-3.23	2.61	2.04-3.34	2.52	1.97-3.23
4 of 4	3.64	2.53-5.25	4.13	2.87-5.96	3.95	2.73-5.69

*Operative year, left ventricular function, extent of disease, and ITA use.

shown). The addition of HDL-c and total cholesterol did not appreciably change risk estimates associated with the deadly quartet and provided no additional predictive power ($p = 0.86$, $p = 0.35$, respectively).

It was necessary to determine whether any one of the deadly quartet components was necessary to the expression of mortality risk. If, for example, diabetes were the one risk factor that was necessary for the expression of mortality risk, then one would expect mortality risk to be muted in the absence of diabetes. Therefore, the mortality risk was estimated sequentially when each component risk was absent. Similar HRs were seen for even a single risk factor in the absence of diabetes (HR = 1.58, CI = 1.29-1.95), obesity (HR = 1.61, CI = 1.31-1.98), hypertension (HR = 1.59, CI = 1.24-2.04) and hypertriglyceridemia (HR = 1.73, CI = 1.61-2.57). Furthermore, we saw little evidence that the particular cluster of risk factors altered mortality risk significantly when at least three factors were present. Hazard ratios ranged from 2.20 (1.49-3.24) with obesity, hypertension and hypertriglyceridemia, to 3.49 (1.96-6.20) with diabetes, obesity and hypertriglyceridemia.

The effects of the remaining deadly quartet risk factors in relationship to obesity were reviewed in detail because of the emphasis placed on obesity in Kaplan's original efforts. The effects of one, two or three risks by obesity status as defined by BMI in the top quartile (>30.0) were estimated. For nonobese patients, the HR for one risk was 1.61 (CI =

1.31-1.98), for two risks 2.07 (CI = 1.64-2.62) and for three risks 2.74 (CI = 1.90-3.96). For obese patients, the impact of additional risk factors was seen for three risks (HR = 2.21, CI = 1.41-3.47), but not one (HR = 0.99, CI = 0.68-1.52) or two (HR = 1.36, CI = 0.86-1.99) additional risks. Nonobese patients were more likely to have no deadly quartet risk factors than obese patients (34% vs. 19%). In contrast, obese patients were more likely to have at least two other deadly quartet risk factors than nonobese patients (38% vs. 21%).

Gender effect. Progressing with the model adjusting for age and surgical variables, gender issues were examined. No evidence was seen of a gender effect on survival after adjustment for age, surgical variables, and the deadly quartet (HR = 0.95, 95% CI = 0.81-1.12, $p = 0.55$). However, the differing presentation characteristics of men and women leave the question of whether men and women experience differential effects from the presence of the deadly quartet risk factors. An interaction term between gender and the sum of the quartet components was statistically significant ($p = 0.01$).

The positive interaction finding provides motivation to examine the effects of the deadly quartet by gender. The progressive increase in presence of deadly quartet components is clear for both men and women. The risk for men progressed from 1.49 (1.20-1.84) to 1.80 (1.43-2.29) to 2.31 (1.74-3.07) to 2.58 (1.53-4.36) as the number of

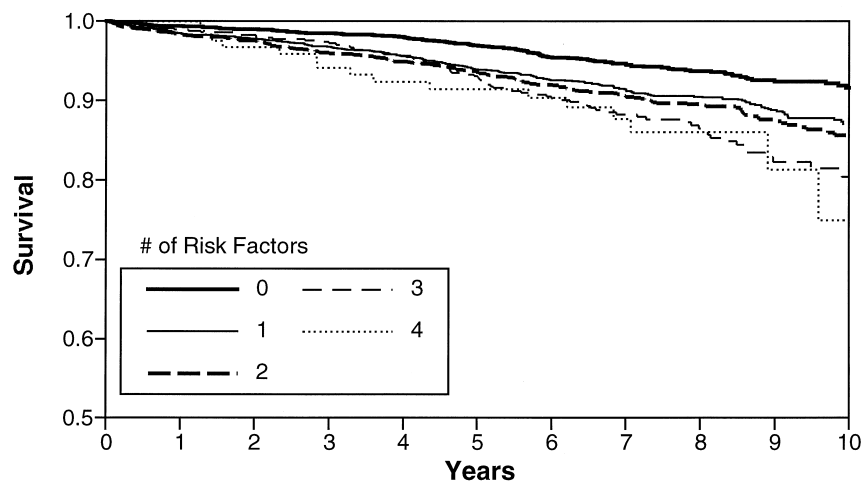


Figure 3. Kaplan-Meier survival curves showing the estimated risk of all-cause mortality for men with 0, 1, 2, 3 and 4 of the deadly quartet risk factors (obesity, diabetes, hypertension and hypertriglyceridemia).

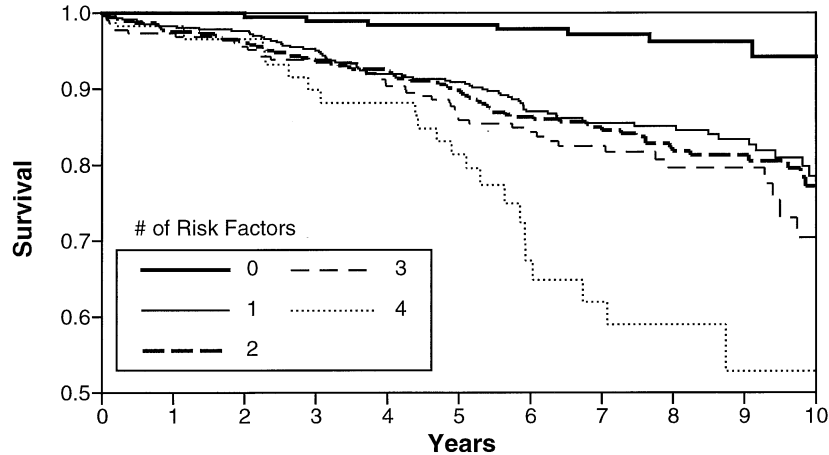


Figure 4. Kaplan-Meier survival curves showing the estimated risk of all-cause mortality for women with 0, 1, 2, 3 and 4 of the deadly quartet risk factors (obesity, diabetes, hypertension and hypertriglyceridemia).

deadly quartet risks increased from 1 to 4 (Fig. 3). The effect was even more dramatic in women as HRs moved from 4.43 (2.04–9.62) to 5.03 (2.31–10.94) to 6.32 (2.85–14.04) to 13.39 (5.66–31.68) as the deadly quartet risk factor sum increased from 1 to 4 (Fig. 4). An examination of the CIs shows that the high end of the 95% CI in men is almost always less than the low end of the 95% CI in women.

DISCUSSION

We have found in subjects with relatively severe coronary atherosclerotic disease and subsequent CABG a striking clustering of metabolic risk factors, previously reported as part of the “deadly quartet”. Over 90% of the 860 patients who died during follow-up had at least one element of the deadly quartet. The concurrent presence of three or more members of the quartet occurs in 10% of men and 21% of women in the pre-CABG population at our institution, and among these groups one in five men and one in four women died over the course of follow up. In contrast, in patients without any of the deadly quartet risk factors, 1 in 10 men died and 1 in 20 women died during the follow-up period. **“Common soil.”** Analysis of a cluster of risk factors, all metabolically interrelated, has not been previously performed in a group of CHD subjects. Although the physiologic lines may be somewhat unclear, this cluster of factors may represent primarily the presence of one disorder, which has multiple clinical presentations (5,8,23). The frequency of those without any of the risk factors is substantially more than expected, and the frequency of those with multiple metabolic risk factors (3 or 4) is increased beyond that expected. Therefore, lack of any members of the cluster is interpreted as lack of the substrate for the disorder, absence of the “common soil” (5) for diabetes and atherogenesis, and clear protection from even expressing one member of the cluster. It does not appear that any single risk factor is pivotal to the expression of mortality risk. In contrast, with

three risk factors, the “soil” for the disorder is fertile, and expression is enhanced.

Gender. We have observed a twofold greater prevalence of this composite in women than in men, suggesting that this metabolic quartet is a more typical basis for vascular disease in women. The individual cardiovascular implications of TG and DM are known to be more relevant in women (19,24). Now, presented herein, when all four risk factors are present in a woman, the risk for death is over 10-fold, compared to a risk of death in a man of two- to threefold. The relatively small number of patients with all four risk factors present leads to fairly wide CIs; however, it appears that women have more risk for death than do men when one or more members of the quartet are expressed, and they have a tendency for reduced mortality when none are present. Indeed, when adjustment is made for this metabolic clustering, no difference in mortality was noted between men and women post-CABG, consistent with results of the Bypass Angioplasty Revascularization Investigation (BARI) (25).

Influence of body mass. Increments in BMI are associated with increasing rates of CHD and mortality (26), and they form a major element of the Kaplan quartet (1). Though some have suggested that body mass is independently correlated with vascular disease, this is difficult to prove owing to the strong interactions with other traditional risk factors (27–29). After dividing patients according to their baseline BMI (< or > 30.0), the composite of the three remaining risk factors markedly decreases in prevalence in those below the top quartile, while the probability of death remains the same (i.e., if you have hypertension, hypertriglyceridemia and diabetes, the risk of death appears similar whether your BMI is high or low). The higher incidence of metabolic clustering with greater BMI suggests that the dramatic trend for increasing obesity in the U.S. is an ominous sign (30).

Summary. Based on recorded information (indeed, the presence of some quartet members may escape recognition or documentation), we have found that a clustering of metabolic features is evident in CAD patients, expressed beyond that anticipated by chance alone. As in subjects without known CAD, those with significant disease—even after the protection of surgical revascularization—suffer a substantial increase in mortality when this syndrome is expressed. Important tools to protect against this risk cluster, e.g., fibric acid derivatives to improve intermediate lipoprotein processing and to decrease TG levels (31), angiotensin-converting enzyme inhibitors to reduce plasminogen activator inhibitor-1 levels (increased in this syndrome) (32–34), decrease sympathetic activity and enhance insulin receptor sensitivity (35), and/or metformin (36) and troglitazone to upregulate insulin sensitivity, are becoming understood and available. Statin therapy in diabetic patients is at least as therapeutic as in nondiabetics (37–39), including post-CABG patients (40), and it should be considered in those with this metabolic cluster. In subjects preparing to have CABG, and perhaps in all those with CAD, expression of members of the deadly quartet can be a prequel to fatal outcomes and should motivate global treatment strategies beyond the simple attention dedicated to the presenting feature of the deadly cluster, especially in women.

Reprint requests and correspondence: Dennis L. Sprecher, The Cleveland Clinic Foundation, 9500 Euclid Avenue, C51, Cleveland, Ohio 44195. E-mail: sprechd@ccf.org.

REFERENCES

- Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 1989;149:1514–20.
- Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–607.
- Genest J, Jr, Cohn JS. Clustering of cardiovascular risk factors: targeting high-risk individuals. *Am J Cardiol* 1995;76:8A–20.
- Yusuf HR, Giles WH, Croft JB, Anda RF, Casper ML. Impact of multiple risk factor profiles on determining cardiovascular disease risk. *Prev Med* 1998;27:1–9.
- Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. *Diabetes* 1995;44:369–74.
- Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham Study. *JAMA* 1979;241:2035–8.
- Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. *Arch Intern Med* 1999;159:1104–9.
- Reaven GM, Chen YD. Insulin resistance, its consequences, and coronary heart disease. Must we choose one culprit? (editorial; comment). *Circulation* 1996;93:1780–3.
- Blomhoff JP. Lipoproteins, lipases, and the metabolic cardiovascular syndrome. *J Cardiovasc Pharmacol* 1992;20:S22–5.
- Despres JP. Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition* 1993;9:452–9.
- Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. *J Chronic Dis* 1979;32:563–76.
- Management of dyslipidemia in adults with diabetes. American Diabetes Association. *Diabetes Care* 1998;21:179–82.
- National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994;89:1333–445.
- The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993;153:154–83.
- Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997;157:2413–46.
- Morris JJ, Smith LR, Jones RH, et al. Influence of diabetes and mammary artery grafting on survival after coronary bypass. *Circulation* 1991;84:III275–84.
- Risum O, Abdelnoor M, Svennevig JL, et al. Diabetes mellitus and morbidity and mortality risks after coronary artery bypass surgery. *Scand J Thorac Cardiovasc Surg* 1996;30:71–5.
- Kurban A, Bowker T, Ilsley C, et al. Differences in the long term mortality of the diabetic and non-diabetic populations in the Coronary Angioplasty vs Bypass Investigation (CABRI) (abstr). *Circulation* 1999;100:1-591.
- Castelli WP. Epidemiology of triglycerides: a view from Framingham. *Am J Cardiol* 1992;70:3H–9.
- Lipid Metabolism Branch Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute: the Lipid Research Clinics Population Studies Data Book. Volume I: The Prevalence Study. Bethesda, Maryland: National Institute of Health Publication 80-1527, July 1980.
- Cox D. Regression models and life tables. *J Royal Stat Soc* 1972;B34:187–220.
- Efron B. The efficiency of Cox's likelihood function for censored data. *J Am Stat Assoc* 1977;76:312–9.
- Taegtmeyer H. Insulin resistance and atherosclerosis. Common roots for two common diseases? (editorial; comment). *Circulation* 1996;93:1777–9.
- Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979;2:120–6.
- Jacobs AK, Kelsey SF, Brooks MM, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1998;98:1279–85.
- Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med* 1999;341:427–34.
- Keys A. Overweight, obesity, coronary heart disease, and mortality: the W.O. Altwater Memorial Lecture, 1980. *Prog Clin Biol Res* 1981;67:31–46.
- Barrett-Connor EL. Obesity, atherosclerosis, and coronary artery disease. *Ann Intern Med* 1985;103:1010–9.
- Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;67:968–77.
- Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 1998;21:518–24.
- Rubins HB, Robins SJ, Collins D. The Veterans Affairs High-Density Lipoprotein Intervention Trial: baseline characteristics of normocholesterolemic men with coronary artery disease and low levels of high-density lipoprotein cholesterol. Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Intervention Trial Study Group. *Am J Cardiol* 1996;78:572–5.
- Vague P, Juhan-Vague I, Aillaud M, et al. Correlation between blood fibrinolytic activity, plasminogen activator inhibitor level, plasma insulin level, and relative body weight in normal and obese subjects. *Metab Clin Exp* 1986;35:250–3.
- Landin K, Stingendal L, Eriksson E, et al. Abdominal obesity is associated with an impaired fibrinolytic activity and elevated plasminogen activator inhibitor 1. *Metab Clin Exp* 1990;39:1044–8.
- Juhan-Vague I, Alessi MC, Vague P. Increased plasma plasminogen activator inhibitor 1 levels. A possible link between insulin resistance and atherothrombosis. *Diabetologia* 1991;34:457–62.
- Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–53.
- Effect of intensive blood-glucose control with metformin on compli-

- cations in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-65.
37. Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992;15:820-5.
 38. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
 39. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997;20:614-20.
 40. Hoogwerf BJ, Waness A, Cressman M, et al. Effects of aggressive cholesterol lowering and low-dose anticoagulation on clinical and angiographic outcomes in patients with diabetes: the Post Coronary Artery Bypass Graft Trial. *Diabetes* 1999;48:1289-94.