ORIGINAL ARTICLE

Differential Improvements in Lipid Profiles and Framingham Recurrent Risk Score in Patients With and Without Diabetes Mellitus Undergoing Long-Term Cardiac Rehabilitation

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ABSTRACT. Carroll S, Tsakirides C, Hobkirk J, Moxon JWA, Moxon JWD, Dudfield M, Ingle L. Differential improvements in lipid profiles and Framingham recurrent risk score in patients with and without diabetes mellitus undergoing long-term cardiac rehabilitation. Arch Phys Med Rehabil 2011;92: 1382-7.

Objective: To determine whether lipid profiles and recurrent coronary heart disease (CHD) risk could be modified in patients with and without diabetes mellitus undergoing long-term cardiac rehabilitation (CR).

Design: Retrospective analysis of patient case records.

Setting: Community-based phase 4 CR program.

Participants: Patients without diabetes (n=154; 89% men; mean ± SD age, 59.6±8.5y; body mass index [BMI], 27.0±3.5kg/m^2) and patients with diabetes (n=20; 81% men; mean age, 63.0±8.7y; BMI, 28.7±3.3kg/m^2) who completed 15 months of CR.

Interventions: Exercise testing and training, risk profiling, and risk-factor education.

Main Outcome Measures: Cardiometabolic risk factors and 2- to 4-year Framingham recurrent CHD risk scores were assessed.

Results: At follow up, a significant main effect for time was evident for decreased body mass and waist circumference and improved low-density lipoprotein cholesterol (LDL-C) level and submaximal cardiorespiratory fitness (all $P<.05$), showing the benefits of CR in both groups. However, a significant group-by-time interaction effect was evident for high-density lipoprotein cholesterol (HDL-C) level and total cholesterol (TC)/HDL-C ratio (both $P<.05$). TC/HDL-C ratio improved (5.0±1.5 to 4.4±1.3) in patients without diabetes, but showed no improvement in patients with diabetes (4.8±1.6 v 4.9±1.6).

Conclusions: We showed that numerous anthropometric, submaximal fitness, and cardiometabolic risk variables (especially LDL-C level) improved significantly after long-term CR. However, some aspects of cardiometabolic risk (measures incorporating TC and HDL-C) improved significantly in only the nondiabetic group.

Key Words: Cardiac rehabilitation; Cardiometabolic risk; Cardiorespiratory fitness; Exercise training; High-density lipoprotein cholesterol; Low-density lipoprotein cholesterol; Rehabilitation; Type 2 diabetes.

SEVERAL RECENT REPORTS from contemporary large international databases, such as the REeduction of Atherothrombosis for Continued Health Registry, showed that stable outpatients with coronary heart disease (CHD), especially those with concomitant diabetes, experience high rates of subsequent CHD events despite the use of various standard medications and medical treatments.[1] International survey data also showed substantial residual cardiometabolic risk in patients with CHD, especially obesity, dyslipidemia, increased blood pressure, and impaired glucose tolerance. These are highly prevalent, largely undertreated, and undercontrolled.[2-4]

The need for intensive, longitudinal, multimodal optimal medical therapy in high-risk CHD groups[5] has been reiterated recently.[6-10] Several studies[11-16] reporting somewhat conflicting results compared the effects of cardiac rehabilitation (CR) between patients with and without diabetes. Moreover, long-term lifestyle–induced improvements in cardiometabolic risk factors in patients with type 2 diabetes without CHD also were inconsistent.[17,18] Therefore, the aim of our study was to evaluate the impact of a 15-month comprehensive outpatient CR program on cardiometabolic and Framingham recurrent risk profiles in cardiac patients with and without diabetes mellitus.

List of Abbreviations

4S	Scandinavian Simvastatin Survival Study
BMI	body mass index
CHD	coronary heart disease
CR	cardiac rehabilitation
CRF	cardiorespiratory fitness
DANSUK	DANish StUdy of impaired glucose metabolism in the settings of cardiac rehabilitation
ECG	electrocardiogram
ETT	exercise tolerance test
EUROASPIRE	European Action on Secondary Prevention through Intervention to Reduce Events
FRS	Framingham risk score
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
RPE	rating of perceived exertion
SCRIP	Stanford Coronary Risk Intervention Project
TC	total cholesterol

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METHODS

Participants

Consecutive referrals were extracted from the Heart Watch community-based phase 4 CR program, Leeds, West Yorkshire, United Kingdom. The program was developed and delivered by Leeds City Council. All eligible patients had a previous clinical diagnosis of CHD and were referred by their general practitioner, consultant cardiologist, or hospital-based CR staff. Written informed consent for exercise testing and training was obtained from all patients. Ethical approval was received from the Leeds Metropolitan University Faculty Ethics Committee.

The CR program consisted of clinical evaluation, exercise testing, risk-factor education, and counseling sessions on an ongoing regular basis. All patients had been discharged from the hospital for at least 12 weeks and were clinically stable, asymptomatic, and deemed capable to self-monitor and regulate exercise training. Patients underwent a baseline clinical evaluation that included medical and cardiac history, anthropometry, blood pressure, lipoprotein-lipid profiles, an electrocardiogram (ECG) at rest, and a submaximal cardiorespiratory fitness (CRF) test that included electrocardiography. Patients were reassessed at 3 and 15 months, including physician review of symptoms and medications and adherence to exercise training. Exercise adherence was confirmed by checking weekly attendance registers of exercise classes.

CR medical staff were not responsible for ongoing therapeutic management, but routinely informed patients' general practitioners of changes in symptoms, adverse cardiometabolic risk, and exercise testing abnormalities. We retrospectively analyzed patient records to evaluate changes in these variables. Our inclusion criteria were patients who (1) had undergone 2 consecutive CRF tests and simultaneous blood tests at baseline and 15 months, (2) presented with a diagnosis of myocardial infarction or CHD or had undergone bypass surgery (coronary artery bypass grafting) or percutaneous transluminal coronary angioplasty, and (3) were nonsmokers. Patients with diabetes had a confirmed diagnosis of type 1 or 2 diabetes mellitus on baseline referral. Patients with other diseases, such as valvular heart disease, peripheral vascular disease, cardiomyopathies, or cardiac arrhythmia syndromes, or those with a pacemaker were excluded. For purposes of our study, patients were stratified into 2 groups: (1) participants without and (2) with diabetes.

Procedures

Anthropometric data, including stature, body mass, and waist circumference, were collected. Waist circumference was measured at the level of the umbilicus, and hip circumference, at the level of the greater trochanters (nearest 0.5cm) by using a flexible tape with the subject standing. Venous blood sampling was conducted between 9.30 AM and 12.30 PM after an overnight fast of at least 12 hours. Blood samples were drawn with minimal venous stasis from an antecubital vein into Monovette[a] serum tubes. From January 1994 to August 1996, lipid analyses were undertaken as routine clinical samples at Seacroft Hospital Biochemistry Department, Leeds, accredited by Clinical Pathology Accreditation (UK). Serum high-density lipoprotein cholesterol (HDL-C) was measured in all normolipemic samples (fasting triglycerides <4.0mmol/L) by using the heparin manganese-chloride method. The laboratory subscribed to the UK National External Quality Assurance Scheme during the study period. Lipid analyses were performed on a Hitachi 747 analyzer[b] using Boehringer Mannheim[b] reagents at the Leeds General Infirmary. HDL-C level was determined by using the polyethylineglycol/aminophenazone method, with coefficients of variation for low and high HDL-C levels of 6.3% to 13.3%. Maximum coefficients of variation for cholesterol and triglyceride levels derived from external quality assurance schemes were approximately 5%. Total cholesterol (TC)/HDL-C ratio was calculated as an index of lipid-associated CHD risk and is supported by both its superior predictive power compared with TC, low-density lipoprotein cholesterol (LDL-C), or HDL-C levels and lower within-person variability.[19]

Systolic (Korotkoff phase I) and diastolic (Korotkoff phase V) blood pressures at rest were determined manually by using a mercury sphygmomanometer.[c] These measurements usually were obtained from the right arm with the subject in a sitting position. The lower of 2 consecutive measurements obtained within 10 minutes was used. The Framingham Recurrent Risk Model[20] (Framingham risk score [FRS] model) was used to determine recurrent CHD risk for 2 and 4 years. The multivariate model included age, sex, TC level, HDL-C level, current smoking status, and presence of diabetes. Systolic blood pressure also was used in only women.

An ECG at rest was obtained with the subject in the standing position before the exercise tolerance test (ETT). The exercise test was conducted on a Marquette Max treadmill[d] using a 2-minute stage incremental protocol.[21] Patients were encouraged to exercise up to 85% of age-predicted maximum heart rate (220−age) or a "very hard" rating of perceived exertion (RPE 17) using the Borg scale.[22] However, the ETT was terminated if a patient presented with symptoms highlighted as contraindications by the American College of Sports Medicine.[23] Submaximal exercise testing was conducted in a nonhospital setting that was medically supervised. Following local cardiologist advice, the higher risk associated with maximal exercise testing in cardiac patients was not considered appropriate for a community environment. Exercise test outcome measures used in the present report were peak heart rate during the final exercise stage completed, highest RPE, and exercise test duration.

Exercise Training Program

The CR program was formally supervised by qualified exercise instructors. The exercise training program was 45 to 60 minutes (including warm-up stretching, aerobic/resistance-based circuit training, and cool-down). Patients were strongly encouraged to walk 30 minutes per day and attend exercise classes on 3 nonconsecutive days per week. The circuit training component involved six 4-minute stations, some with 8 different exercises. Aerobic exercise included floor and treadmill walking, leg cycling, arm-leg cycling, rowing ergometry, and bench-stepping. Resistance and floor-based sets comprised 8 different exercises performed for up to 30 seconds each. All patients wore a heart rate monitor[e] during exercise. Exercise intensity was modified for each patient according to exercise heart rate and electrocardiographic responses. Patients were expected to exercise to 40% to 85% of their submaximal heart rate reserve (peak treadmill exercise heart rate minus heart rate at rest), which was monitored by the exercise instructors.

Statistical Analysis

Continuous variables were presented as mean ± SD, and categorical data, as percentage. An arbitrary level of 5% statistical significance was used throughout (2 tailed). Independent *t* tests and chi-square analysis were used to identify differences in variables and proportions on cardioprotective therapies between the nondiabetic and diabetic groups at base-

line. Independent-samples *t* test was used to identify baseline differences between groups. To identify potentially significant group-by-time interactions, separate (group × time) analyses of variance with repeated measures for time were used, and when applicable, Bonferroni post hoc analysis was conducted. Additional subgroup analyses were undertaken (1) excluding all participants for whom lipid-lowering medication status changed during the follow-up period and (2) for participants not on statin therapy throughout the duration of the study. SPSS software, Version 17.0[†] was used for statistical analyses, and significance was assumed at $P<.05$.

RESULTS

Patients without diabetes (n=154; 89% men; mean age, 59.6±8.5y; body mass index [BMI], 27.0±3.5kg/m^2) and patients with diabetes (n=20; 81% men; mean age, 63.0±8.7y; BMI, 28.7±3.3kg/m^2) completed 15 months of CR. All baseline diagnostic, anthropometric, metabolic, and exercise variables are listed in table 1. Patients with diabetes tended to be older and showed a more adverse anthropometric profile (higher BMI and waist circumference). However, there were no significant baseline differences between patients with and without diabetes in any variables except for 2- and 4-year FRSs (both $P=.001$) and a significantly higher prevalence of statin therapy at baseline in patients without diabetes (42% vs 29%). Self-reported exercise training compliance rates at 15 months, reported on clinical reassessment, were similar between groups (diabetic group, 3.0±1.5 compared with nondiabetic group, 2.9±0.9 sessions/wk). Exercise test results showed that treadmill duration increased from 10.1 to 12.2 minutes in patients without diabetes and 8.8 to 10.4 minutes in patients with diabetes (both $P<.05$). Peak RPE and submaximal heart rate attained on the treadmill test did not differ between groups at baseline and follow-up (see table 1).

A main effect for time was evident for anthropometric variables (decreased body mass and waist circumference), LDL-C level (decreased), FRS at 4 years (decreased), TC level (decreased), and cardiorespiratory fitness (increased submaximal exercise test duration; $P<.05$ in all cases), showing the benefit of exercise training in both groups at follow-up (see table 1). A trend toward lower diastolic blood pressure at rest over time also was evident ($P=.069$).

A group-by-time interaction effect was evident for HDL-C level and TC/HDL-C ratio ($P<.05$). In patients without diabetes, TC/HDL-C ratios improved from baseline (5.0±1.5) to 15 months (4.4±1.3). In contrast, TC/HDL-C ratio showed no improvement in patients with diabetes (4.8±1.6 vs 4.9±1.6). FRS at 4 years improved in the nondiabetic (17.1%±3.4% vs 15.1%±4.1%) and diabetic groups (22.2%±4.1% vs 21.6%±5.0%). A significant group effect (nondiabetic group lower than diabetic group) was evident for FRS ($P<.05$). We adjusted our analyses to examine any influence of statin therapy. A subgroup analysis was performed on all patients with no change in statin therapy at 15 months (nondiabetic group, n=128; diabetic group, n=16). This included patients for whom statin therapy was unchanged and those not prescribed statins at any point. We found that the interaction effect remained (all $P<.05$) for HDL-C level, TC/HDL-C ratio, and FRS at 4 years. The analysis was re-run for all patients not on statin therapy at baseline and with no change in statin therapy status at follow-up (nondiabetic group, n=71; diabetic group, n=10) (table 2). A group-by-time interaction effect was evident for HDL-C level in this subgroup of patients ($P<.05$). In patients with CHD, HDL-C levels improved from baseline (1.18±0.34mmol/L) to 15 months (1.27±0.40mmol/L). HDL-C levels decreased in the diabetic group (1.22±0.31 vs 1.09±0.25mmol/L). However, no significant time or interaction effect in TC/HDL-C ratio or FRS at 4 years (P for interaction effect=.125 and $P=.087$, respectively) was observed (data not shown). The proportion of participants using diabetic medication was unchanged (see table 2).

DISCUSSION

We showed that anthropometric and submaximal fitness variables and LDL-C levels improved significantly in both the nondiabetic and diabetic groups after long-term (15mo) CR incorporating structured aerobic/resistance exercise training. Most

Table 1: Anthropometric, Metabolic, and Exercise Test Variables: Baseline and 15-Month Follow-up in Patients Without and With Diabetes

Variable	Baseline Nondiabetic	15 mo Nondiabetic	Baseline Diabetic	15 mo Diabetic	Repeated-Measures ANOVA *P*		
					Time	Group	Time × Group Interaction
BMI (kg/m^2)	27.0±3.5	26.8±3.5	28.7±3.3	28.3±2.9	.084	.058	.403
Body mass (kg)	79.0±12.0	78.8±12.3	83.4±11.3	81.7±10.1	.033	.201	.125
Waist circumference (cm)	95.2±9.6	94.4±9.5	101.5±8.9*	98.6±7.3	.001	.018	.054
Systolic BP at rest (mmHg)	143.3±20.0	141.3±20.8	150.0±25.0	145.2±17.8	.133	.224	.536
Diastolic BP at rest (mmHg)	85.6±11.2	83.8±9.4	86.7±11.2	83.6±14.8	.069	.835	.622
HR at rest (beats/min)	66.5±14.3	65.5±12.5	72.9±16.8	73.3±15.7	.570	.014	.376
TC (mmol/L)	5.48±1.01	5.14±0.89	5.36±1.49	5.09±1.05	.007	.681	.734
HDL-C (mmol/L)	1.17±0.30	1.24±0.34	1.15±0.25	1.09±0.22	.842	.211	.023
Triglycerides (mmol/L)	1.82±1.26	1.60±0.86	2.11±1.01	2.10±1.26	.312	.092	.377
LDL-C (mmol/L)	3.54±0.93	3.20±0.82	3.37±1.23	3.18±0.92	.011	.629	.472
TC/HDL-C ratio	4.98±1.51	4.40±1.28	4.84±1.60	4.91±1.59	.074	.535	.024
Exercise HR peak (beats/min)	126.6±19.0	128.9±18.5	128.9±24.3	129.1±22.3	.467	.773	.542
Exercise RPE peak	14.7±1.9	15.2±1.7	15.1±1.5	15.2±1.9	.282	.633	.509
Exercise duration (min)	10.1±2.7	12.2±2.7	8.8±3.2	10.4±3.5	<.0001	.011	.323
FRS, 2 y (%)	8.5±2.4	7.9±2.2	11.5±2.7*	11.5±2.8	.123	<.0001	.055
FRS, 4 y (%)	17.1±3.4	15.1±4.1	22.2±4.1*	21.6±5.0	.114	<.0001	.051

NOTE. Values expressed as mean ± SD unless noted otherwise. Patients without diabetes, n=151; patients with diabetes, n=20.
Abbreviations: ANOVA, analysis of variance; BP, blood pressure; HR, heart rate.
*Significant baseline differences between patients without and with diabetes ($P<.05$).

Table 2: Proportions of Patients Using Diabetic and Cardioprotective Medications and Attainment of Therapeutic Control of TC, BP, and Clinical Obesity in Accordance With Professional Society Guidelines (Joint European Society/EUROASPIRE Surveys): Baseline and 15-Month Follow-up in the CAR and CDM Groups

Variable	Baseline		15 mo	
	Nondiabetic	Diabetic	Nondiabetic	Diabetic
Diabetic medication (%)	NA	39	NA	46
Statins (%)	40	35	51	45
β-Blockers (%)	42	46	41	46
ACE inhibitors (%)	19	23	27	23
Diuretics (%)	16	31	16	31
TC (<4.5mmol/L)	18	35	23	25
Systolic BP (<140mmHg)	38	40	43	35
Diastolic BP (<90mmHg)	56	45	70	70
BP (<130/80mmHg)	12	10	12	25
BMI (<30.0kg/m^2)	80	75	80	70

NOTE. Values expressed as %.
Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; NA, not applicable.

inpatient and outpatient CR programs or exercise training studies typically ranged from only 6 weeks[24] to 3 months.[14,25,26] We found that HDL-C level improved in the nondiabetic group after comprehensive CR. We report significant increases in the proportion of patients prescribed statin therapy, which increased by approximately 10% in patients with and without diabetes. These changes in coronary risk factors were consistent with earlier reports,[11,26] including a randomized controlled trial[17] showing lipid improvements, except for HDL-C level in 1 study.[11] An earlier short-term study showed similar nonsignificant changes in risk factors in a large cohort of patients with diabetes.[13]

Our findings are consistent with other multimodal intensive interventions that significantly improved cardiometabolic risk factors. Favorable intervention changes in cardiometabolic risk compared with relatively small changes in the usual-care group also were shown in the randomized Stanford Coronary Risk Intervention Project (SCRIP) 4-year study.[27] However, only a small proportion of patients with diabetes were randomly assigned (10%–13%) in SCRIP. Lifestyle changes were more effective than metformin for decreasing the incidence of diabetes in high-risk patients with impaired glucose metabolism.[28,29] In secondary prevention settings, a 12-month Danish study investigated stepwise intensive CR (DANish StUdy of impaired glucose metabolism in the settings of cardiac rehabilitation [DANSUK]),[30] including an initial 6-week period of supervised exercise training, on risk-factor profile in 104 patients with type 2 diabetes or impaired glucose tolerance. Participants were randomly assigned to hospital-based rehabilitation compared with usual care. In patients with diabetes, waist circumference, TC level, and LDL-C level (−3% and 9.6%, respectively), but not triglyceride and HDL-C levels, decreased significantly compared with the usual-care group. Of note, proportions of patients in the DANSUK usual-care and intervention groups receiving statin therapy at study end were high (82% and 94%, respectively).

Consistent with other reports, our patients with diabetes had significantly lower exercise capacity than patients without diabetes at baseline[13,14,24] and had similar relative improvements with exercise training. An increase of 1mL·kg^{-1}·min^{-1} in peak oxygen uptake is equivalent to a 9% decrease in cardiovascular-related mortality in secondary prevention settings.[31] Although we did not measure maximal oxygen uptake, we found an improvement in mean submaximal oxygen uptake of 3 to 4mL·kg^{-1}·min^{-1}, or approximately 1 metabolic equivalent.[23] Recently, Mourot et al[24] reported similar short-term improvements in exercise capacity after a multidisciplinary CR program in a large cohort of patients with CHD with and without type 2 diabetes. This generally was consistent with other studies that reported improvements of 38% in patients with diabetes and 34% in patients without diabetes after 3 months of exercise training[24] or 26% in patients with diabetes after 10 weeks of training.[13] Verges et al[12] reported less impressive improvements in peak oxygen uptake after 2 months of aerobic training (13% in patients with diabetes). Likewise, exercise capacity did not significantly improve in patients with type 2 diabetes in the CR group compared with usual care in DANSUK.[30] It is not clear why these discrepancies exist; however, it likely is caused by a number of factors, including differences in participant baseline characteristics (age, medication use, disease severity, prevalence of comorbid conditions, volume/intensity of exercise training), training adherence, and CRF measurement methods.

Based on the FRS, we showed that risk for a recurrent cardiac event within 4 years decreased after 15 months in the nondiabetic group compared with patients with diabetes. The higher risk reported in the diabetic group was consistent with previous findings. A revised Framingham CHD risk score[32] also decreased significantly in the intensive intervention group in SCRIP compared with usual care. However, in the present investigation, only approximately 20% of study participants attained the Joint European Societies treatment target for TC level (<4.5mmol/L). In comparison, the proportion with increased cholesterol levels decreased from 94.5% in European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) 1 (1995–1996) to 42.6% in EUROASPIRE III (2006–2007), largely because of the increased use of statins. Likewise, the mentioned intensive CR studies reported end-study statin therapy rates consistently in the region of 90% in CR patients or active intervention groups.[26,27]

Clinicians should consider more aggressive lipid lowering (statin monotherapy or combination regimens)[33,34] and angiotensin-converting enzyme–inhibitor therapy in patients with CHD, especially those with diabetes, to improve cardiometabolic risk and estimated cardiovascular endpoints. However, several studies showed cardiometabolic risk profile to deteriorate significantly after short-term CR on long-term follow-up.[35,36]

Study Limitations

Several important study limitations should be highlighted. First, this was a retrospective analysis of patient case records. Patients were recruited over a considerable time frame, many before the publication and widespread dissemination of the benefits of several cardioprotective therapies in secondary prevention settings and professional society guidelines. Only 13% of our sample (all without diabetes) was recruited before publication of the Scandinavian Simvastatin Survival Study (4S).[37] Most participants (84%), including most patients with diabetes, were recruited between the seminal publication dates of the 4S and subsequent Heart Protection Study[38] in 2002. Only 5 participants were recruited post-2002. Participants were not randomly, assigned and both selection and referral bias may be present. We were not able to provide a comparison control group of cardiac patients not undergoing exercise training intervention. Accordingly, the influence of regression to the mean for cardiometabolic and cardiorespiratory fitness variables should be considered. Most patients referred for rehabil-

itation were men, and the findings may not be generalizable to female outpatients without diabetes. In this cohort, referred patients with diabetes constituted only a small proportion of patients and relatively few completed 15 months of CR. The first EUROASPIRE survey (1995–1996)[39] also reported low representation of both women and patients with diabetes (20.7% and 17.4%, respectively). It also is important to consider that the FRS is not without limitations. The risk algorithm was derived from the original Framingham cohort, predating many medical and surgical treatment advances for secondary prevention of CHD. Obesity and associated conditions such as diabetes were far less prevalent in the cohort of patients with preexisting cardiac disease in the original Framingham study.[20] Other important risk factors in secondary prevention, such as ischemic history, other vascular comorbid conditions,[2] cardioprotective medications, and contemporary risk biomarkers (such as N-terminal pro-brain natriuretic peptide or high-sensitivity C-reactive protein) were not considered. Finally, although our study showed improvements in Framingham recurrent risk estimation, it was not designed to assess subsequent cardiovascular events. Further studies of larger cohorts with longer follow-up are required to show subsequent clinical prognosis in patients with and without diabetes.

CONCLUSIONS

We showed that numerous anthropometric, submaximal fitness, and cardiometabolic risk variables (especially LDL-C level) improved significantly after long-term CR. However, some aspects of cardiometabolic risk (measures incorporating TC and HDL-C levels) improved significantly in only the nondiabetic group. Optimal medical therapy, a healthy lifestyle with regular physical exercise, and coronary interventions are interdependent treatment strategies.[40] This long-term outpatient community-based CR program appeared efficacious in decreasing residual risk in CHD groups.

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