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Typical and atypical coronary heart disease deaths and their different relationships with risk factors. The Gubbio residential cohort Study

Paolo Emilio Puddu [a,*], Oscar Terradura Vagnarelli [b], Mario Mancini [c], Alberto Zanchetti [d], Alessandro Menotti [e]

[a] Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatric Sciences, Sapienza University of Rome, Viale del Policlinico 155, I-00161 Rome, Italy
[b] Centre of Preventive Medicine, Gubbio, Italy
[c] Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy
[d] Istituto Auxologico Italiano, University of Milan, Milan, Italy
[e] Associazione per la Ricerca Cardiologica, Via Latina 49, I-00179 Rome, Italy

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ABSTRACT

Objectives: The Seven Countries Study showed that fatal coronary heart disease (CHD) with only chronic heart failure, arrhythmia or blocks (atypical CHD, A-CHD) may represent a distinct disease as compared to fatal CHD cases with *angina pectoris*, acute myocardial infarction (AMI) or sudden death (typical CHD, T-CHD). We aimed at validating this, using identical diagnostic criteria, in a separate residential cohort first examined in 1983–85 in Gubbio, central Italy.

Material and methods: Forced Cox's models were run to assess 9 classic risk factors and their 20-year predictivity of A-CHD versus T-CHD, in the entire cohort or separately for men and women.

Results: There were 3229 subjects aged 30–79 years. Entry mean age was slightly higher in women than men although age at death was lower in men than in women for both T-CHD (71.99 ± 11.38 versus 81.20 ± 9.35 years, $p < 0.0001$) and A-CHD (80.22 ± 9.44 versus 84.98 ± 8.13 years, $p < 0.0001$). T-CHDs were predicted by male gender, age, continued smoke, systolic blood pressure (SBP), blood glucose, total and HDL-cholesterol (protective). A-CHDs were predicted by age, continued smoke, SBP, body mass index and blood glucose but neither total nor HDL-cholesterol or gender was significant. In the entire cohort and in men there were predictive differences of T-CHD versus A-CHD fatalities only in relation to age ($p < 0.01$), SBP ($p < 0.05$) and total cholesterol ($p < 0.01$).

Conclusion: As age, SBP and total cholesterol had a different predictive role of T-CHD versus A-CHD fatalities also in the Gubbio cohort, the possibility is reinforced that a different etiology exists between these entities.

1. Introduction

Coronary heart disease (CHD) may present clinically either with symptoms (*angina pectoris*, acute myocardial infarction, AMI, with either ST segment elevation or not, the latter being the modern counterpart of the intermediate syndrome of the past) or with painless manifestations (chronic arrhythmia and blocks and congestive heart failure) whereas sudden death is closer to the first than the second category [1]. The availability of specific biological tests has tremendously increased the diagnostic accuracy of AMI [2]. However, the abovementioned symptomatic and asymptomatic categories may have much less distinct boundaries when diagnostic criteria are applied in longitudinal epidemiological studies [3]. On the other hand, precise boundary definitions among different CHD clinical presentations are not provided by the most updated in vivo imaging modalities [4] specifically directed to coronary plaques [5] nor by *post mortem* anatomo-pathological studies [6–9].

Reports from the Seven Countries Study, a classic of international cardiovascular epidemiology [10,11], showed that fatal cases where the presentation among 10,628 men initially aged 40–59 years during 40 years of follow-up was only congestive heart failure, chronic arrhythmia, blocks or with the generic mention of chronic CHD (arbitrarily called atypical CHD, A-CHD) were not predicted by serum cholesterol [12–14]. On the opposite, fatal CHD cases manifested with *angina pectoris*, AMI, acute ischemic attack or sudden death (arbitrarily called typical CHD, T-CHD) showed a strong positive association between serum cholesterol and events. Moreover, there was a stronger association with age for A-CHD than for T-CHD [12–14]. Therefore, the

* Corresponding author at: Laboratory of Biotechnologies Applied to Cardiovascular Medicine, Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatric Sciences, Sapienza University of Rome, Viale del Policlinico, 155, Rome 00161, Italy. Tel.: +39 06 49972659; fax: +39 06 4453891.
E-mail addresses: paoloemilio.puddu@uniroma1.it (P.E. Puddu), oscar.terradura@gmail.com (O. Terradura Vagnarelli), mariomancini30@virgilio.it (M. Mancini), alberto.zanchetti@unimi.it (A. Zanchetti), menottia@tin.it (A. Menotti).

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hypothesis was raised that A-CHD may represent a distinct disease as compared to T-CHD [14].

The aim of the present study was the external validation of the Seven Countries Study results whereby the differential relationship of A-CHD and T-CHD with age and total cholesterol was obtained [12–14]. It is in fact essential in epidemiological studies to try to repeat in independent cohorts the evidence obtained in one investigation [15–17]. We took advantage of a common thread of shared investigators between the Seven Countries Study [10–16] and the Gubbio Cohort Study [18–21]. We applied identical methods for case definitions and we extended the applicability of the results since we also investigated women (not included in the Seven Countries Study) yet assessing very long follow-up periods. The null hypothesis was that A-CHD and T-CHD deaths share identical risk factors and are predicted indistinctly by those factors entering significantly a forced Cox's model during 20 years of follow-up.

2. Material and methods

2.1. Population, risk factors and mortality data

The Gubbio Cohort Study is a population study devoted to cardiovascular diseases conducted in the small town of Gubbio in central Italy. The original sample, first examined in 1983–1985, covered the entire population living within the ancient medieval walls, including both genders and ages 5 to 95 (n = 5376), with a participation rate of 92.2%. For the purpose of this analysis only men and women aged 30–79 were considered, for a total of 3553 subjects.

A number of potential risk factors were measured at entry examination, as follows:

- gender (coded as 0 and 1 for women and men, respectively);
- age in years at the time of the visit;
- body mass index (BMI in kg/m^2) following the procedures suggested by the WHO Cardiovascular Survey Methods Manual [22] for the measurement of height and weight;
- systolic blood pressure in mm Hg, measured by a trained personnel, following the procedure described by the WHO Manual [22]; in particular, participants were in sitting position, a mercury sphygmomanometer was used and the first measurement was taken after a 5 min rest; three measurements were recorded, and the average of the second and third measurement was used for analysis; the physicians taking the measurements were trained and tested using the tape-recorded procedures of the London School of Hygiene;
- serum total cholesterol (mg/dl), high-density lipoprotein (HDL) serum cholesterol (mg/dl), and fasting plasma glucose (mg/dl) measured using automated enzymatic methods [23,24]; the laboratory involved in these analyses was under quality control of the WHO Lipid Reference Center of Prague; controls included also duplicate blinded analyses on at least 10% of all laboratory samples;
- Cigarette smoking habits were derived from a standard questionnaire and people were classified in 3 dummy variables, i.e. current smokers, ex-smokers and never smokers, the last one used as reference.

Mortality data were collected through the end of 2007 with a mean follow-up of about 20 years. Information was obtained from the local register office and review of medical records and interviews with spouses or baystanders and coded by a single reviewer (AM) using the ninth revision of the WHO International Classification of Diseases (WHO-ICD-9) [25]. This was the same person responsible for coding fatalities in the Seven Countries Study [12–14]. In case of uncertainty among apparent multiple causes of death, a hierarchical system was adopted giving precedence to violent causes, cancer in advanced stages, CHD, stroke and other causes in that order. The first cause of death was used for this analysis. The end-point for the analysis was cases of CHD classified into 2 groups:

- Typical coronary heart diseases (T-CHDs) were cases coded as AMI, acute coronary ischemic attacks, *angina pectoris* and sudden death, after reasonable exclusions of other causes;
- Atypical coronary heart diseases (A-CHDs) were cases classified as congestive heart failure, arrhythmia, blocks and ill-defined chronic CHD (without other specifications), in the absence of AMI, other ischemic attacks, *angina pectoris*, sudden death or other explicit etiologies.

Subjects who carried CHD (including cases with previous coronary surgery), other forms of heart disease, cerebrovascular disease and peripheral artery disease at entry examination were excluded from the analysis (n = 324: prevalent cases).

Among the remaining 3229 subjects there were missing data for some of the risk factors selected for this analysis. Therefore, they were imputed by a multivariate normal procedure using as reference the personal characteristics with full data. This process was based on a regression analysis using the variable containing the missing value as the dependent variable and all variables with non missing data in that row as independent variables. The values of these non missing variables from the row containing the missing values are used in the regression equation to compute the imputed values. The proportion of missing values was relatively small (2.3%) and no difference was found between the means of the original and the imputed values. No significant difference was seen in the variance of the overall sample, compared with the original one.

Oral consent was obtained from the participants in compliance with the Helsinki declaration.

2.2. Statistical analysis

Data are presented as mean ± standard deviation or standard error (as appropriate) and minimum, maximum and range values. Death rates from T-CHD and A-CHD were computed for overall subjects and separately for men and women, including standardized rates for the two genders based on the overall age distribution. Age at death was computed for the two end-points, for the entire cohort and separately for men and women. Cox proportional hazards models were solved (after assessing the proportionally of hazards) using T-CHD and A-CHD fatalities separately and 9 risk factors (gender, age, smoking and ex smoking habits, systolic blood pressure, body mass index, blood glucose, serum total and HDL cholesterol) as possible predictors adopting the forced methods (all covariates were in the Cox's model at step zero), in order to compute their individual relative contribution. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using standard formulae. For continuous covariates, deltas corresponded approximately to 1 SD whereas the absolute range was considered for dichotomous covariates. T-tests were adopted to test the difference between coefficients of T-CHD versus A-CHD fatalities. Figures were drawn to show the relationship of age, serum cholesterol and systolic blood pressure with T-CHD and A-CHD deaths. Significance was concluded for p values <0.05.

3. Results

Baseline descriptive statistics are shown in Table 1 for 3229 individuals aged 30–79 (mean age 52.92 ± 13.16) years. There were 1433 men (44%) and 1796 women (56%). During approximately 20 years of follow-up T-CHD and A-CHD death rates were respectively 5.30 and 3.98% ($p = 0.3009$) in men and 3.40 and 4.73% ($p = 0.0531$) in women. T-CHD rates were higher in men than in women ($p = 0.0101$) whereas A-CHD rates were similar ($p = 0.3440$). Heart failure was present in 49.3% of A-CHD deaths either as an explicit cause of death or it was annotated among the symptoms present before death. There was also a significant entry mean age difference in men and women, respectively 51.50 ± 13.06 and 53.85 ± 13.16 years ($p < 0.0001$) with a significantly lower age at death in men ($p < 0001$) than in women ($p = 0.0014$) for both T-CHD (71.99 ± 11.38 versus 81.20 ± 9.35 years, $p < 0.0001$) and A-CHD (80.22 ± 9.44 versus 84.98 ± 8.13 years, $p < 0.0001$).

Table 2 shows HR and 95% CI of forced Cox's model solutions, to predict T-CHD and A-CHD fatalities in the entire cohort and in males and females. In the entire cohort, T-CHDs were predicted by male gender, age, continued smoke, systolic blood pressure, blood glucose, total cholesterol and HDL-cholesterol (the last being protective); A-CHDs were instead predicted by age, continued smoke, systolic blood pressure, body mass index and blood glucose. Notably, in A-CHD, neither total cholesterol nor HDL-cholesterol or gender had a significant role. There were significant differences for age ($p < 0.01$), systolic blood pressure ($p < 0.05$) and total cholesterol ($p < 0.01$) in their predictive capacities of T-CHD versus A-CHD fatalities whereas the remaining covariates considered had a comparable predictive role for either T-CHD or A-CHD. This picture was confirmed in males and females, although the smaller numbers introduced some discrepancies. For example in women, in whom convergence for A-CHD was obtained only after removing body mass index and blood glucose, the predictive capacities of T-CHD versus A-CHD fatalities were different only for age ($p < 0.01$), there was no difference for systolic blood pressure and total cholesterol had only a borderline significantly different role ($p < 0.0674$).

Fig. 1 illustrates the 20-year risk of death whereby it is clearly shown that starting at age 55 years there is a dissociation between A-CHD and T-CHD risk curves, the former steeply increasing with age. On the other hand, Fig. 2 shows that the 20-year risk of T-CHD death is a function of serum cholesterol levels, but the reverse is true in the case of A-CHD death. These differences are in contrast with those of systolic blood pressure where trends, differentiating T-CHD versus A-CHD deaths,