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RESEARCH ARTICLE

Heart Diseases of Uncertain Etiology: Epidemiological Observations Compared with Clinical Experience

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ABSTRACT

Backgrounds and Aims: Simple, long-term epidemiological observations allowed to identify a heterogeneous group of heart diseases manifested only as heart failure, arrhythmia and blocks in the absence of typical coronary syndromes, that we arbitrarily called initially atypical Coronary Heart Disease (CHD) and then Heart Disease of Uncertain Etiology (HDUE) in 12 published investigations.

Methods and Results: This group of heart diseases covered about 20% of all CVD mortality and about 10% of all-cause mortality in population cohorts close to extinction and compared with typical CHD was characterized by a strong association with age and the absence or an inverse association with serum cholesterol, dietary habits and physical activity. Moreover, HDUE appeared at an older age and had a higher age at death. Blood pressure and smoking habits (the latter with some uncertainties) were directly associated with the disease. Old pathology findings had already segregated the large myocardial scars due to gross atheroma of coronary arteries from small multiple sclerotic/fibrotic scars that seem independent and unrelated to coronary atheroma.

Conclusion: Etiology of HDUE, although probably multiple, is still vague and elusive, and the Literature was little informative about its relative frequency and possible causality. Future investigations might be stimulated by this review. To segregate HDUE from CHD should be important to correctly assess relationships among multiple risk factors and differential or condensed outcomes.

Keywords: Atypical CHD; HDUE; risk factors; age at death; outcome; etiology

INTRODUCTION

The term Heart Diseases of Uncertain Etiology (HDUE) is an operational, arbitrary label given by our research group to the pool of some heart diseases investigated within epidemiological studies that apparently could not be classified by clear etiological characteristics. Although this contribution is not a "standard" review article, we put our epidemiological results in perspective of what is reported in the Literature, particularly from the clinical point of view. In doing so, we aim to give insight into one of the most urgent and important question facing clinicians globally across the many different fields of health sciences mainly when they refer to congestive heart failure (CHF) which was the most common manifestation of what we call HDUE as a group and is abundantly investigated in the Literature but no way to find etiologic elements that should be contrasted with coronary heart disease (CHD) as is the case here, based on objective and measured risk factors that compete [1-15], specifically from the epidemiological point of view.

In fact, we have been stimulated by the almost absent attention in the Literature (both on population and clinical basis) for heart diseases that cannot be clearly classified on the basis of the International Classification of Diseases and Cause of Death and are simply described as symptomatic heart diseases or, within some classes have characteristics largely different from those of the majority that share typical syndromes. Moreover, we noticed too frequently that when searching for risk factors or causes, largely different types of cardiovascular diseases are pooled together, simply because they belong to the same anatomo-physiological system although likely different from the etiological point of view. It would be the same approach and mistake as searching a common etiology and risk factors for the entire digestive system (from pharynx down to rectum) simply because the several tracts belong to the same system.

The purpose of this contribution is to give a summary of findings that we obtained during several years based on population studies and to try to find an interpretation reviewing some problems of nomenclature and classification, some pathological findings and contributions, especially from the clinical Literature that could identify possible etiologies for those cases.

In other words, this contribution is not a systematic review of the Literature, but simply a short summary of 12 papers based on our epidemiological experience together with an attempt to search in the Literature for what could be the etiologies and/or major risk factors of this group of heart diseases mainly based on the clinical experience developed elsewhere.

SUMMARY OF PERSONAL OBSERVATIONS

Our research group has been involved in a number of population studies in different countries and for long follow-up periods, mainly focusing on Coronary Heart Diseases (CHD) [1-15].

The structure of the various studies was rather similar consisting in the enrollment of population samples located in several countries, like in the Seven Countries Study of Cardiovascular Diseases[1-4,6,7,14], the Italian Rural Areas (IRA) of the same study [5,9-13], the Gubbio Population study run in a small town of central Italy [8], and the RIFLE Project run on 45 population samples in various Italian regions [15]. Analyses on those four studies covered more than 12000, around 1700, around 3500 and more than 47000 subjects, respectively.

The first two studies included only men, the other two both genders with variable age ranges but usually covering middle-aged people. A baseline examination including a variable number and type for personal characteristics and risk factors mainly focused on those of cardiovascular nature was followed by systematic follow-up for mortality and causes of death and in the IRA also by incidence of major cardiovascular diseases. The duration of follow-up ranged from about 7 years up to 50 years. The main structure of the analyses was made by running multivariable models with cardiovascular events as end-point and various types of risk factors as predictors.

Initially, the criteria for the definition of CHD, mainly for mortality, partly for incidence, were rather flexible and sensitive, in order to include many cases, but not so highly specific. Later, the need was felt to use more specific criteria in order to identify true CHD events that finally included only cases manifested as myocardial infarction, acute ischemic attacks and sudden coronary death. Among the remaining heart diseases we disregard those that were etiologically defined or very rare, such as congenital and rheumatic heart diseases, non-rheumatic valvular diseases, pericarditis, endocarditis, myocarditis, cardiomyopathies, pulmonary heart diseases, ill-defined heart diseases, and other rare conditions.

The residual heart diseases were made by a heterogeneous pool of cases, poorly classified, including hypertensive heart diseases usually not well documented by accompanying left ventricular hyperthrophy, cases manifested only as heart failure, arrhythmia or blocks (Symptomatic heart

diseases according to the International Classification of Diseases) and cases vaguely classified as chronic or other types of CHD but not accompanied by typical coronary syndromes described above. In general, symptomatic heart diseases, chronic CHD and hypertensive heart disease covered about 65%, 25% and 10% respectively of all HDUE. Incidentally, in preliminary tests, the three components were separately analyzed and proved to have similar characteristics. Initially, this group was called "atypical - or only possible - CHD", but after a number of comparative analyses versus CHD, this subgroup was arbitrarily called HDUE (Heart Diseases of Uncertain Etiology).

Detailed results are reported in the original articles, while here we provide a summary of the main findings. Several differences were found between the two groups (CHD versus HDUE), with HDUE having a stronger relationship with age, appearing at older ages, having a definitely higher age at death, initially manifesting preferably with non-fatal heart failure, having a flat or inverse relationship with serum cholesterol and HDL cholesterol, and a neutral relationship with vigorous physical activity and healthy diet [4-15]. The predictive role of blood pressure and cigarette smoking was relatively similar comparing CHD to HDUE. A summary of the differences found between these two groups mainly focusing on serum cholesterol is given in Table 1. Findings were rather uniform across different locations and countries, and different length of follow-up. Marginal exceptions were the not significant role of serum cholesterol for CHD in Japan [14], probably due to the small samples and the limited number of events, and the limited difference in age at death between CHD and HDUE in the RIFLE project [15] likely due to the short follow-up duration preventing the population to enter definite older ages.

Table 1. Summary of findings comparing CHD with HDUE derived from 12 previous published Studies, focusing on the role of serum cholesterol and age at first event or age at death.

Bib Ref (year)	*Study*	Location	N Sex age	FU and end-point	CHD/HDUE ratio	Cholesterol CHD	Cholesterol HDUE	Age at death or first event	Other risk factors
4 (1998)	SCS 16 cohorts	USA, Finland, the Netherlands, Italy, Former Yugoslavia, Greece, Japan	12761 Men Age 40-59	25 years mortality	2.1	HR = 1.24 (s) in North America and Northern Europe HR=1.23 (s) in Southern Europe HR =0.9 (ns)7 in Japan	HR= 1.0.5 (ns) in North America and Northern Europe HR= 10.4 in Southern Europe (ns) HR= 0.93 in Japan (ns)	CHD = 65.8 HDUE = 70.2	---
5 (2005)	SCS 2 cohorts	Italy	1712 Men Age 40-59	40 years mortality	2.1	HR= 1.26 (s)	Excluded in step wise procedure	CHD = 74.1 HDUE = 76.4	---
6 (2005)	SCS 10 cohorts	Finland, the Netherlands, Italy, Serbia, Greece	6633 Men age 40-59	35 years mortality	3.1	HR 1.22 (s)	HR 0.90 (ns)	CHD = 71.6 HDUE = 75.8	---
7 (2013)	SCS 13 cohorts	USA,Finland, the Netherlands, Italy, Serbia, Greece,Japan	9704 Men Age 40-59	40 years mortality	3.3	HR 1.31 (s)	HR 0.90 (ns)	CHD = 72.6 HDUE = 77.6	---
8 (2014)	Gubbio population study	Italy	3229 men and women Age 30-79	20 years mortality	1.48	HR 1.29 (s)	HR = 0.87 (ns)	CHD =72.0 HDUE = 81.2	Plasma glucose predictive in both conditions HDL cholesterol only in CHD Triglycerides not predictive
9 (2015)	SCS 2 cohorts	Italy	1712 CVD free men	50 years incidence first event	1.3	HR = 1.22 (s)	HR = 1.02 (ns)	----	---

10 (2015)	SCS 2 cohorts	Italy	1712 men Age 40-59	50 years incidence first event	---	---	---	CHD = 68.9 HDUE = 74.3	---
11 (2015)	SCS 2 cohorts	Italy	1712 men Age 40-59	Up to the age of 90 years (31 to 50 years) first event	1.6	---	---	---	-HR vigorous physical activity Vs sedentary CHD 0.67 (s) HDUE = 0.78 (ns) -HR Mediterranean Diet Vs Non Mediterranean Diet CHD = 0.62 (s) HDUE = 0.91 (ns)
12 (2016)	SCS 2 cohorts	Italy	1712 men aged 40-59	50 years mortality	1.97	----	----	----	-HR vigorous physical activity Vs sedentary CHD 0.68 (s) HDUE = 0.84 (ns) -HR Mediterranean Diet Vs Non Mediterranean Diet CHD = 0.53 (s) HDUE = 0.88 (ns)
13 (2016)	SCS 2 cohorts	Italy	1712 men Age 40-59	50 years mortality	----	Analysis of competing risks with Fine Gray method showing that Cholesterol was the critical risk factor segregating CHD from HDUE		----	----
14 (2019)	SCS 13 cohorts	USA, Finland, the Netherlands, Italy, Serbia, Greece, Japan	10628 men age 40-59	45 years mortality	2.5	HR = 1.21 (s)	HR = 1.05 (ns)	CHD = 73.5 HDUE = 79.1	---
15 (2019)	RIFLE Pool of 45 cohorts	Italy	25272 men 21895 women age 35-74	7.4 years mortality	1.47	HR 1.24 (s)	HR = 1.03 (ns)	CHD = 60.7 HDUE = 61.0	Plasma glucose (s) in both conditions HDL cholesterol only in CHD Triglycerides not predictive

SCS = Seven Countries Study; HR for cholesterol for a difference of 1mmol/L, (s)= significant; (ns) not significant at p =< 0.05. Systolic blood pressure and cigarette smoking were similarly predictive of both endpoints.

In the case of HDUE (or any other possible term used to define it), a clear etiology could not be identified but, apparently, little efforts have been made in the available Literature to identify it, despite its frequency that, in almost extinct male populations of the Seven Countries Study, represents around 10% of total mortality and 20% of cardiovascular mortality [14]. Overall, not only the relationships of serum cholesterol with HDUE and CHD were different but also their baseline mean levels: baseline mean serum cholesterol was of 235 mg/dl in future CHD deaths versus 199 mg/dl in future HDUE deaths [5]. This may mean that, everything else being equal, that difference of 36 mg/dl is associated with a delay of about 5 years in the occurrence of a fatal heart disease, CHD coming first, HDUE only later with a 5-year longer expectancy of life.

Overall, the main characteristics of HDUE cases are occurrence at older age compared with CHD, no relation with cholesterol levels, and perhaps no association with healthy diet and vigorous physical activity, while some conflicting evidence was shown for cigarette smoking.

Figure 1 presents the different occurrence of HDUE versus CHD during subsequent time periods in the Italian Rural Areas of the Seven Countries Study originally made of 1712 men aged 40-59 years with a follow-up (for this analysis) of 51 years broken down into three 17-year periods. It clearly appears that mortality from HDUE is rather low during the first period, then increasing and overtaking CHD mortality in the third period.

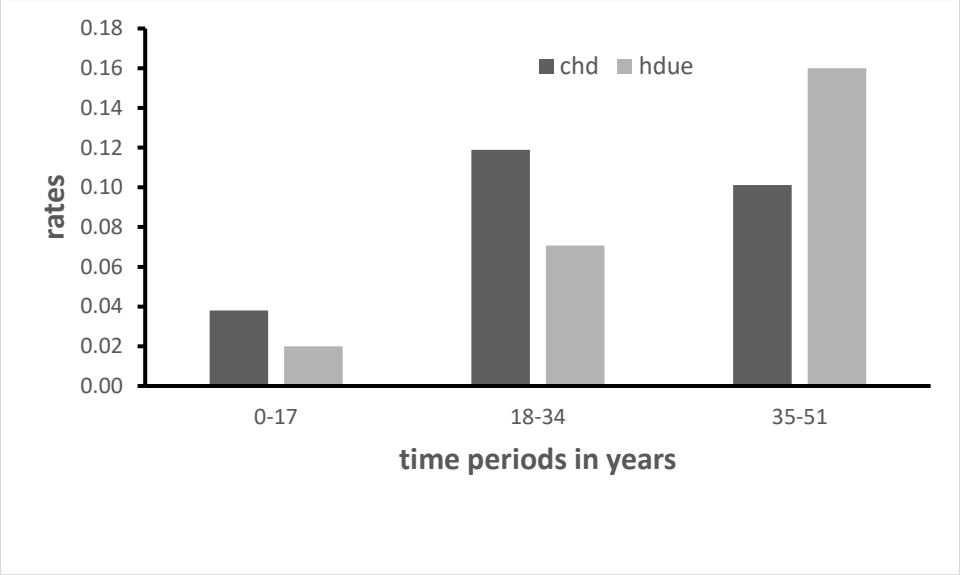

Figure 1. Death rates from HDUE and CHD in the Italian Rural Areas of the Seven Countries Study during 51 years of follow-up broken down into three 17-years periods. Note that initial denominator was made of 1626 cardiovascular disease-free men aged 40-59. Subsequent rates are computed on men alive at the beginning of each time period, i.e. 1626 for period 0-17: 1203 for period 18-34; 494 for period 35-51.

Some of these documented conclusions, based on relatively recent epidemiological evidence, were somewhat anticipated by a prototypal paper published in 1965, that is 35 years before the first paper of the recent series. It posed the same questions, based on simple clinical criteria of painful (typical) and painless (atypical) CHD cases and showed the different age distribution and the diverse serum cholesterol levels in simple Italian hospital and outpatient clinics casuistics of the early 1960's [16]. At those times, cases we now call HDUE were frequently classified as "myocardial sclerosis", a term that is vague but partly reflects the idea. Limitations of these conclusions are bound to the fact that collection of data in our studies and analyses were largely located in the second half of last century when modern diagnostic tools were not yet available and to possible diagnostic mistakes due to incompleteness of information. In fact, diagnoses were mainly based on history, clinical examination, ECG tracings, review of clinical records and interviews, plus official mortality data. However, similar findings were obtained in different circumstances, geographical locations and cultures, for short and long follow-up periods, for both incidence and mortality and for both genders.

These coherent findings prompted the idea to find out what could be the possible etiologies or at least risk factors of these conditions considering the limitations of the diagnoses posed in epidemiological field work started last century and going on for more than 50 years. This was made analyzing the evolving classification of heart diseases, inspecting some old but valuable pathology findings, reviewing some epidemiological and clinical Literature. We make clear that in this procedure we were not interested into the pathophysiology of heart failure, arrhythmia or blocks, that are syndromes that can develop during the natural history of any heart disease, focusing instead on the possible etiologies and/or risk factors of cases where clear etiology cannot be identified. This approach includes the search on how frequently these syndromes are classified as an unknown cause.

HDUE, NOMENCLATURE AND CRITERIA

HDUE is only an operational term to index, based on epidemiological criteria available in the second half of last century, a group of heart diseases whose etiology could not be clearly identified. This group is surely heterogeneous since it probably includes different cardiac syndromes or manifestations. Some of them, such as heart failure, chronic arrhythmia and blocks do not identify a specific etiology but they can be pathophysiological steps occurring during the natural history of any defined heart disease. On the other hand, we included into this group also cases vaguely classified as hypertensive heart disease and chronic and "other types" of CHD, for reasons explained in previous reports [4-15].

Classification and definition of cardiovascular diseases (CVD) in epidemiological studies and analyses are not univocal. Heart diseases are usually segregated from other major CVD conditions such as stroke and peripheral artery diseases. However, it is not always clear what heart diseases mean, while they should probably at least be subdivided into CHD and other heart diseases, a distinction that is not always clearly stated. Frequently all kind of CVD are considered in a single group, including all possible diseases of the heart and circulatory system, independently from the respective and largely different etiologies. Usually CHD is defined by WHO-ICD-9 codes 410-414 [17] or by codes I20-I25 of the WHO-ICD-10 [18] but the meanings of codes called "other forms of ischemic heart disease", "other acute ischemic heart disease" and "chronic ischemic heart diseases" are somewhat confusing or at least not explicit, although they represent an improvement of code 412 (chronic ischemic heart disease) of the previous ICD-8 classification [19]. Nowadays, objectively, the WHO ICD-10 classification [18] is universally used in clinical and scientific practice and a reasonable description can be found of the several components of Ischemic Heart Disease but, again, some components of code I25 (chronic ischemic heart disease) are still open to misinterpretations.

In epidemiological reports, choices of code groups is not always fully proper since they do not always take into account the possible etiology. For example, in a large meta-analysis of serum cholesterol versus CVD [20] the following groups were considered: (a) all circulatory diseases, (ICD-9 codes 390 to 459) that cover all possible conditions of all possible etiologies, with the only exclusion of congenital heart diseases (that are classified in the section of congenital malformations); (b) ischemic heart disease [ICD-9 codes 410-414 + 798 (sudden death)] including also chronic ischemic heart diseases that, on the basis of our experience, are not predicted by serum cholesterol and have a higher age of occurrence and age at death, compared with the other CHD codes. Moreover, it should be noted that code 798 represents sudden death, independently from any type of validation since it was assumed that all those cases were of coronary origin; (c) stroke in all its forms; (d) all the other heart and circulatory diseases again irrespective of possible different etiologies. In any case, the problem of possible different etiologies (and risk factors and natural history) of unidentified cases was never posed from the etiologic point of view. There are many examples of this type and all of them might have suffered of this clinically acritical choice of disease groups, based only on the international classification. This also means that the large majority of cases that we call HDUE cannot be identified in the current Literature and indeed a real interest was never evident to dissociate them from classical CHD cases.

A major difference between most contributions in the cardiovascular epidemiological field and our own studies is that, for over half of fatal events in the SCS and the Italian Rural Areas (IRA), beyond the availability of death certificates, we could exploit also information from repeated field examination (including ECG tracings), clinical records from hospital and other sources, interviews with family and hospital doctors and with relatives of the subjects and any other possible source of information. The same information, apart from death certificates, was available for not fatal events, not relying on externally determined ICD codes. This approach probably allowed a better identification and classification of CVD and other causes of death, at least within the limits of the epidemiological procedures, anticipating by years the concept and structure of the Verbal Autopsy Instruments produced by the WHO many years later [21]. Still a large proportion of heart diseases could not be classified in a precise etiological group.

Part of the problems of nomenclature and classification was tackled by expert study groups of the World Health Organization and the International Society and Federation of Cardiology that tried, in the second part of last century to provide criteria for the definition and classification of heart diseases mainly for epidemiological purposes [22-25]. Despite many uncertainties, the suspect was posed that a diagnosis of CHD (or ischemic heart disease) manifested without the occurrence of typical syndromes (such as angina pectoris, acute ischemic attack - or the

correspondent terms used in the past -, myocardial infarction, sudden death and in the absence of clear etiology) should be classified outside the typical CHD group. In a position report of 1979 [25] it was stated that in cases with heart failure, in the absence of clear coronary syndromes, the diagnosis of CHD should remain only presumptive. This concept heavily contradicted a previous position of the investigators of the Evans County population study in the USA, where cases of heart failure in people aged 40 years or more, in the absence of reasonable causes, should be classified as CHD [26].

OLD PATHOLOGY FINDINGS

A convincing evidence on the possible existence of two different diseases (as those that we call CHD and HDUE) can be found in very old pathology papers [27-29]. Those analyses showed that the size of myocardial scars had a bimodal distribution, that large scars were strongly associated with gross atheroma, thrombosis of large coronary vessels and myocardial infarction, while this was not the case for small scars that, among other things, were not more common among cases carrying large scars. The hypothesis was made that infection, toxic or allergic agents and other unknown causes could be responsible for cases with multiple small scars that lead to diffuse sclerosis of the myocardium with fibrotic muscle replacement [29] and, possibly later, to heart failure. The potential involvement of apoptosis in the origin of myocardial scars and sclerosis was later raised [30], but this is probably a pathogenetic step more than an etiological factor.

CONDENSED REVIEW OF LITERATURE

A review of the Literature has been performed in order to identify hypothetical etiologies of cases that we have classified as HDUE from the epidemiological experience, based on selected references derived from total of about 3000 articles found in PubMed in late 2019 to early 2021.

Since the majority of our cases of HDUE had heart failure as first manifestation we initially focused on this condition. We could not find many examples giving the frequency of heart failure of unknown cause, both in clinical and population studies run in Western Countries [31-38]. Usually, the majority of cases were attributed to CHD like in the Evans County experience [26]), while those of unknown origins varied from 15 to 37%. Little attention was given to the possible causes but frequently high blood pressure was considered a valuable risk factor [36-39]. This probably means that in Western Countries the major cause of heart failure is CHD while for a substantial proportion of cases a clear etiology cannot be found, still admitting the limited diagnostic tools in some of the environments where the studies were run. The picture seems entirely different in African countries [40-42] or other developing countries [43] where CHD is still rare and the major role for developing heart failure is attributed to hypertension, rheumatic heart disease and some specific African cardiomyopathies of uncertain etiology.

Instead, in review papers, the possible "causes" of heart failure (in general) were described in a chaotic way, including a mix of established heart diseases, such as myocardial infarction and valvular heart disease, more or less traditional risk factors of heart diseases such as dyslipidemia (classified as a minor risk factor), hypertension, together with dietary factors, smoking habits and sedentary life style, diabetes, obesity, and findings of diagnostic procedures, such as left ventricular hypertrophy, ECG abnormalities, carotid wall thickness [44,45]. In the above list, several items have nothing to do with etiology, classic risk factors or determinants since they are established CVD conditions of different types or partial diagnostic data that in their natural history can evolve into Heart Failure.

In other analyses of population studies, including a reappraisal of the Framingham Study [46], and others in the USA [47], Sweden [48] and Japan [49], levels of serum cholesterol were not (or even inversely) correlated with the occurrence of heart failure but only in the Japanese study a clear segregation of ischemic from non-ischemic cases was done showing the presence of an inverse association with heart failure only in cases of non-ischemic heart disease and a direct one in cases of CHD (myocardial infarction).

During the last 15-20 years several clinical studies suggested that low levels of serum cholesterol were associated with a poor prognosis in advanced stages of heart failure. Among the few quoted here as examples [50-57], only two [53, 54] were clearly limited to heart failure due to non-CHD patients. Probably the above conclusions are confounded by the association of low serum cholesterol with malnutrition in elderly people with heart failure, but the problem has nothing to do with prediction or etiology of events or mortality in subjects initially free from an etiologically defined heart disease. Altogether, it was easy to conclude that the search of causes or at least risk factors of heart failure in the absence of a clear etiology never arose much interest, despite its apparent high frequency.

The group of heart diseases more recently defined as Non Ischemic Cardiomyopathies (NICM) [58,59] could be among those included into our group of HDUE and they frequently manifest with severe arrhythmia. Actually, the term of NICM is inconsistent (like Ischemic Cardiomyopathy that is only a "synonymous " of CHD or IHD) since it simply negates the existence of ischemia. In the Literature there are no studies to identify in a reliable way its frequency while data are available only as isolated and highly selected hospital casuistics. A long and heterogeneous series of possible causes are listed such as rare mitochondrial abnormalities [60], molecular genetic patterns associated with different types of NICM (hypertrophic, dilated, arrhythmogenic) [61], genes linked to heart failure or at least to its severity [62], alcohol addiction inducing the dilated type of cardiomyopathy [63,64], whose frequency in one report is given as 21-36 % of all NICM [63], cocaine addiction [65], and the role of diabetes [66,67].

DISCUSSION AND CONCLUSIONS

Simple, long-term epidemiological observations mainly made in the second part of last century allowed to identify a heterogeneous group of heart diseases manifested only as heart failure, arrhythmia and blocks in the absence of typical coronary syndromes, that we arbitrarily called HDUE. They included cases classified as symptomatic heart diseases, ill-defined hypertensive heart diseases and cases of "chronic coronary heart diseases" in the absence of typical coronary syndromes. Our attention was attracted by the fact that the pool of these cases is quite large and in terms of mortality covers around 20% of all CVD mortality and around 10% of all cause-mortality in population settings followed-up until 50 years, This group of heart diseases, when compared with typical CHD, was characterized by a stronger association with age, (i.e appearing at older ages and having a greater age at death), the absence or an inverse or flat association with serum cholesterol and no relationship with dietary habits and physical activity. Blood pressure and smoking habits (the latter with some uncertainties) were directly associated with the disease called HDUE. These different characteristics pointed to the decision to give a name to this group of CVD that despite some difference showed several common characteristics. In the Literature it was impossible to identify a description of this type of CVD except rare mentions of the relative proportion of heart failure of undefined etiology still lacking a deeper documentation of their characteristics versus CHD or other CVD.

In terms of possible etiology or at least of relevant risk factors, the most evident fact is the absence of serum cholesterol as a risk factor for HDUE, tending to exclude a gross coronary atherosclerosis at the level of conductive vessels.

Therefore, the culprit of this situation could be the population levels of serum cholesterol since people with low levels might be spared from the occurrence of CHD but becoming more prone to develop HDUE several years later prolonging in this way their expectancy of life. This fact might suggest a case of competing risks that in the Italian IRA study has been already documented [13]. In this analysis the use of a predictive model specific for the evaluation of competing risks (Fine-Gray variant of the Cox model) showed the critical role of serum cholesterol that was directly associated with CHD events and inversely associated with other causes of death in a 50-year follow-up.

Literature does not offer much information on what we call HDUE from the epidemiological and etiological points of view. In terms of clinical medicine, conditions called NICM probably correspond to what we mean by HDUE, but no systematic data really exist about its relative frequency and etiology. In fact, information from the Literature is scattered through case reports on single etiologies whose relative frequencies cannot be estimated in a systematic way. Moreover, the absence of relationships with serum cholesterol, diet, and physical activity, age of onset and age at death are never mentioned. This suggests that the bulk of NICM has not yet been sufficiently and systematically explored from the point of view of etiology, causes and risk factors.

Myocardial fibrosis is probably the pathology basis for HDUE in many cases. Old pathology findings had already segregated the large myocardial scars due to gross atheroma of coronary arteries from small multiple sclerotic/fibrotic scars that seem independent and unrelated to coronary atheroma. Difficulties and differences in the approach to the problem may have added incomplete understanding of the issues.

Etiology of HDUE, although probably multiple, is still vague and elusive, and the need of a systematic search seems of great importance. Future investigations might be stimulated by this review. We believe it essential to segregate HDUE from CHD when relationships are investigated among risk factors and outcomes either individually or when multiple definitions (like in case of CVD) are adopted for both mortality and incidence as dilutions may thus appear to impact on results and conclusions.

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