Coronary heart disease incidence and competing risks: an important issue

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1 Introduction

The estimation of lifetime morbid events is not a rare presentation of relatively old and of more recent epidemiological investigations,[1–13] accompanied by evaluating rates, risks and predictors (more in general determinants or risk factors). However, when the follow-up period is very long and Kaplan-Meier survival curves are adopted, or Kaplan-Meier-based more complex models such as Cox’s analysis are used, clinical (or epidemiological) reality may well be distorted since by these survival methods risks tend to be overestimated, whereas survival tends to be reduced.[13–15] For example, it was calculated in a 50-year long follow-up of a residential population of Italian men that the sum of coronary heart disease (CHD) incidence (both fatal and non-fatal) and of any other cause of death was much more than one,[13] a situation that largely overestimates the reality. Therefore, to overcome these difficulties, it is necessary to rather use the so-called competing risks-based methods, that is to investigate the effect of morbid and/or fatal conditions that are alternative (and in competition) with the basic studied condition.[13–18] Special procedures were thus proposed to estimate survival correctly, using in particular the cumulative incidence function (CIF) and the Fine-Gray model.[14–18] Using these models, the CIF of the identical condition expressed above for the Kaplan-Meier situation becomes indeed less than one, as expected when there are still survivors.[13]

When the age ranges of the investigated population extend to the elderly, further problems are met due to the common competition between CHD as events of primary interest and mutually exclusive deaths from any other cause as secondary events.[13,19,20] The results of a recent investigation using the Fine-Gray model among 1677 middle-aged men enrolled in the 1960’ and followed-up for half a century, thus reaching the practical extinction of the initial cohort at ages of death of 76.1 ± 9.9 years[19] among CHD incident individuals, showed that cholesterol was significantly and positively related to the incidence of CHD when the competing condition was death from any other cause.[13] On the other hand, when the primary events were deaths from any other cause and the competing risks were CHD incident events, cholesterol was inversely and age positively related. In the latter case, cholesterol appeared as the discriminant predictor between CHD events and deaths from any other cause, since the large majority of measured covariates by Cox model analysis were both predictors of CHD events and of deaths from any other cause and there was not an opposite mathematical sign for the coefficient of cholesterol.[13]

2 Why it is important to take competing risks into account

One may wonder why it is so important to adopt any type of competing risks analysis, when the follow-up is very long (say more than 40 years) and age ranges enter high elderlyness. The reason rests on the fact that the longer the follow-up, the higher the average age of the initially enrolled population and the higher the likelihood that events, other than those considered of primary interest, come into play to compete with the latter.[18] It has to be underscored, however, that apart from a few epidemiological investigations, experiences whereby follow-up lasts over 40 years are rare.[1,4–7,10–13] In particular, in the predictive domain of CHD in general, competing risks analyses are not generally performed.[21–29] A paper of 2005[30] tried to disentangle the role of some CHD risk factors between the occurrence of myocardial infarction, stroke and venous thrombo-embolism. Hypertension, high serum cholesterol, diabetes and smoking habits were associated with myocardial infarction and stroke but not with venous thrombo-embolism that was associated
with body mass index and height. By applying the competing risks procedure in risk functions produced for predictive purposes among elderly individuals (up to 90 years), more recent investigations improved predictions of CHD and stroke events during follow-up of around 20 years.

A peculiar aspect for enabling the outperformance of competing risks analysis might be the similarities of the primary as compared to the secondary (namely those in competition) events. It was speculated that when risks in competition are closer, meaning that primary and secondary events share some aetiologic factors, for example CHD versus stroke or cardiovascular diseases at large that all have an atherosclerotic origin, the common predictive roles of some risk factors might still be seen by Fine-Gray models. The opposite might be true when there is a contrast between the specific pathology under investigation (for example CHD) with a series of competing events that, all together, represent occurrences that compete largely (in case these are deaths from any other cause) with the atherosclerotic aetiology of CHD.

Current literature has given little attention to these problems, with few noticeable exceptions. This contrasts with the importance of the scientific query that should be addressed. In fact, the probability of a given type of events is heavily influenced by concomitant events that might happen among the exposed individuals. The classic example that is done is a car accident competing with the probability of sinking at seaside when people go on vacation: if one has a car accident on road he may not reach the shore and this reduces the probability of sinking. Clearly, when the follow-up becomes very long and there is an increase in the age ranges of the exposed populations, it becomes essential to adopt the competing risks analyses in order to correctly address the risks of those who will not be censored but will have a different event as compared to the event of primary interest. When the competing events are very distant from the aetiological point of view, this problem becomes even more important. Clearly, this is an area where new statistical methods for assessing accuracy (like AUC ROC) should also be developed to appropriately take into account the risk competition.

3 Applicability to elderly populations with higher risk of ischemic syndromes

It was stressed that in aging populations the proportion of secondary events undergoes a steep increase in numbers. Investigations on the natural history of CHD pointed that CHD manifestations were the cause of death among 68.1% of individuals with CHD events during a life-long follow-up, although 12.7% died from cancer and cancers were the cause of death among only 40.4% of individuals with any other event apart typical or atypical CHD. In these situations of very long follow-up and aging population, the respective role that baseline covariates may have in segregating the probabilities of two types of events in contrast with each other might be shown only by using a competing risks analysis. Therefore, the conclusion that cholesterol was the factor positively related to the incidence of fatal and non-fatal CHD and negatively related to mortality from any other cause, by using the Fine-Gray model, during half a century of follow-up among middle-aged men and that age was more positively associated with mortality from any other cause than CHD, should be regarded as an important suggestion for the critical role of serum cholesterol in discriminating between the two types of events.

The extensive role of cardiovascular risk factors in increasing the risk of events other than CHD and more in general for predicting all-cause mortality was repeatedly stressed. Lifestyle habits might largely impact all-cause mortality and among other potential causes, such as socio-economic development (including smoking habits and physical activity and/or the availability of effective drugs) and diet, cardiovascular risk factor differences may cooperate to explain the large differences existing for example among Eastern and Western European countries in CHD prevalence and incidence. The direct correlation between total cholesterol levels with CHD incidence and mortality is universally recognized. What is more provocative is whether diet and lifestyle changes (including smoking habits and possibly variable control of high blood pressure) might indeed impact and eventually modify the atherosclerotic burden that may be causative of long-term events, independently of lesion severity. These relations are important in all countries but critical among transitional countries, in particular among Eastern European countries.

If one considers geographic distribution of deaths in Europe, cardiovascular diseases represent the main cause of death for women in all countries; it causes more than 50% of deaths in women in 29 countries, mostly in Central and Eastern Europe. It also causes more than 50% of deaths in men in ten countries and all are from Eastern Europe: Azerbaijan, Belarus, Bulgaria, Georgia, Montenegro, Romania, FYR Macedonia, Romania, Ukraine and Uzbekistan. Death rates from CHD are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe. For example, the death rate for men aged under 65 years living in the Russian Federation is more than
13 times higher than in France, and for women it is almost 16 times higher. Western European countries generally have higher rates than Southern European countries: the death rate for both men and women aged under 65 living in Ireland is 1.7 times higher than in Italy.[40] In order to compare quality of care and outcomes following acute coronary syndromes in Central and Eastern European transitional countries an important review of papers published from November 2003 to February 2014 was recently undertaken and 17 papers fulfilled the search criteria.[41] Of the 19 Eastern European transitional countries investigated, data were lacking for four countries. In-hospital mortality for patients with acute myocardial infarction ranged from 6.3% in the Czech Republic to 15.3% in Latvia. In-hospital mortality for ST-elevation myocardial infarction ranged from 3.0% in Poland to 20.7% in Romania. Primary percutaneous coronary intervention in acute myocardial infarction ranged from 1.0% to over 92.0%, fibrinolytic therapy from 0 to 49.6%, and no reperfusion therapy from 7.0% to 63.0%. Therefore, not only in terms of overall cardiovascular and CHD mortality large differences are present in Eastern versus Western countries,[36,37,40] but also wide variation in emergency reperfusion strategies for ST segment elevation acute myocardial infarction suggests that acute cardiac care is likely to be modifiable and if addressed could reduce mortality from acute coronary syndromes[41] and subsequently overall cardiovascular disease deaths[40] in Eastern European transitional countries.

4 Conclusions

It was outlined that the collection of acute coronary syndrome care and outcomes data across Europe must be prioritized.[25,28,41,42] A very good example of what should be done and of current research in Eastern European transitional countries comes from the experience of the ISACS-TC study. This is a registry of all acute coronary syndromes (both ST segment elevation acute myocardial infarction, non ST segment elevation acute myocardial infarction and unstable angina) in a large number of Eastern European countries in transitional economy.[25–29,42] An extensive list of clinical, angiographic, therapeutic and outcome parameters were obtained. Timing from symptoms to hospitalization and to the different treatments were also monitored. Thus, the ISACS-TC registry should be a good comparative basis for performing analyses with Western European databases and/or other registries in different transitional countries in East Asia or South America.[43] It is anticipated that results obtained there, especially indexing outcome[27,29,32] and/or in relation to specific therapeutic regimens,[44,45] might be compared with those obtained in Western countries and be of help in elucidating causes of Eastern versus Western European CHD differences in either treatment or outcome. It will be extremely important to conduct research on CHD related incidence also assessing gender and age-group differences and to compare with other causes of death such as stroke or cancer.

In this paper, we have addressed the notion of potentially applying analytical models that take into consideration competing risks such as Fine-Gray’s CIF analysis.[13–15] Although it is clear that these models should be applied when the follow-up duration is very long, examples exist whereby very short duration follow-up were considered and these models were used.[58] The aetiological proximity between outcomes might be seen as an element whereby to test these models adequately,[13] although other elements should be the gender composition and the age-ranges of the explored populations.[28,29,43] Applying these methods will ultimately enable the creation of adequate profiles on which efforts should be concentrated.

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