The effect of correcting for troponins on trends in coronary heart disease events in Finland during 1993–2002: the FINAMI study

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Aims The object of this study is to analyse the trends in coronary events in Finland during 1993–2002, correcting for the effect of troponins.

Methods and results A population-based myocardial infarction register recorded all coronary events (n = 14 782) in four geographical areas of Finland during 1993–2002. Correction coefficients for the effect of troponins were calculated on the basis of 4359 coronary events, with simultaneous determination of troponins and the ‘old’ enzymatic markers of myocardial injury. Coronary mortality declined steeply, except in women aged ≥75 years. The incidence of first coronary events declined 2.0% (95% confidence interval −3.0, −0.9%) per year among men and 1.0% (−2.7, 0.6%) per year among women aged 35–74 years. After correcting for the effect of troponins, also the decline among women became statistically significant: 2.7% (−4.5, −0.8%) per year. The effect of troponins tended to be stronger in women and older individuals than in men and younger individuals. The 28-day case fatality declined among men, but not among women. The effect of troponins on case fatality trends was weak.

Conclusion Declining trends in the incidence of coronary events in Finland during 1993–2002 were partly hidden by the effect of troponins. Both incidence and case fatality declines have contributed to the decline in mortality.

Introduction

Monitoring of trends in coronary heart disease events is of utmost importance for assessing the disease burden to the community and for evaluating the effects of primary and secondary prevention efforts as well as the impact of changing treatment patterns of acute coronary events. The adoption of new and more sensitive biomarkers of myocardial injury, such as cardiac troponins, during the latter half of the 1990s has, however, posed challenges for consistent monitoring. It is generally known that, because of their greater sensitivity, troponins detect myocardial infarctions (MIs) that cannot be detected with the enzymatic markers of myocardial injury. However, as troponins are also more specific than the enzymatic markers, a fraction of events diagnosed with enzymes as MIs turns out to be false positives when troponins are used. The net effect of these changes on the trends in incidence and case fatality of MI events is not known.

Studies assessing the effects of troponins on the number of MI events have been relatively small and usually of insufficient size to examine whether the effect differs by age or sex.²⁻⁴ Our earlier study suggested that troponins may increase the number of MI diagnoses more in women than in men,⁵ but the effect of age is even less well known. In general, our knowledge about the trends in MI events in persons aged ≥75 is insufficient, although it is a growing population segment and the majority of events occur in that age group. For example, the World’s largest study on coronary heart disease event trends, the WHO MONICA Project,⁶ did not consider people aged >64.

The present paper analyses the trends in coronary heart disease mortality, the incidence of first ever coronary events, and case fatality in populations of four geographical areas in Finland during the 10-year period 1993–2002. An important aim was to ‘correct’ the incidence and case fatality trend estimates for the effect of troponins to see whether important changes might have been hidden by the
adoption of troponins during the latter half of our study period. The other important aim was to compare the event trends among the elderly with those in persons aged 35–74 to see to what extent the favourable development during the recent years has extended to the older age groups.

Methods

FINAMI is a population-based MI register, which operated on four geographical areas of Finland during the period 1993–2002. It aimed to evaluate all events suspected to be an MI or coronary death among the permanent residents of the monitored areas. The geographical areas covered by the FINAMI register were the town of Turku in southwestern Finland, the town of Kuopio in eastern Finland, the town of Joensuu and some adjacent rural areas in eastern Finland, and the town of Oulu in northwestern Finland. Oulu joined in the project later and had data for the years 1993, 1997, 1999, 2001, and 2002, whereas for the other areas, data were available for the whole 10-year period, except for Turku for the year 1999 and Kuopio for the year 1998. However, the age group ≥75 years was consistently included only from the year 1995 onwards. The combined population aged ≥25 of the FINAMI areas is 313,000.

Trained nurses, together with register physicians, collected the information from hospital documents, death certificates, autopsy reports, and medico-legal documents, using standardized data collection protocols. The local registration teams periodically sent their data to the coordinating centre at the National Public Health Institute, Helsinki, where the data were checked for logical errors. Annually, the data were further cross-checked for completeness with the National Causes-of-Death Register and the National Hospital Discharge register. These country-wide registers cover all deaths of the permanent residents of Finland and every hospitalization in Finland. They were linked to our study data using the personal ID-code, unique to every resident of Finland. Events identified through cross-checking and not included in the register were sent back to the local registration teams, which retrieved the necessary documents and evaluated the event according to the study protocol for possible inclusion in the register.

The events were classified on the basis of symptoms, ECG and biomarker findings, and possible autopsy results as suggested in the American Heart Association Scientific Statement of 2003. Definite, probable, and possible fatal and non-fatal MI events were included in the present study. The period of one event was 28 days, during which the most severe findings were recorded. The biomarkers used in each case were determined according to the usual practices of the hospital in question at each point in time. The values of troponin T or troponin I were classified as diagnostic, normal, or missing on the basis of the limits given in the laboratory of the hospital in question. The local register physician evaluated the relevance of troponin elevations using all available clinical information. If the troponin value was considered non-relevant, e.g. because of the timing of the sampling or because of other concomitant diseases such as renal insufficiency, it was taken as missing. The other biomarkers were classified according to the principles of the WHO MONICA Project.

The event was considered as incident (first for the particular patient) if there was no indication of a previous, clinically recognized MI in the patient’s history. Attack rate was defined as the sum of first and recurrent MI events. The 28-day case fatality was defined as the proportion of fatal events from all events. One-year case fatality was calculated for 28-day survivors, i.e. 29-365-day case fatality. Cardiovascular disease deaths were used as the endpoints for 28-day and 1-year case fatalities. Information on 28-day deaths was collected as part of the FINAMI register. Deaths during the 1-year follow-up were identified through the National Causes-of-Death Register, which is known to be of good quality. Thanks to the use of this national register, the follow-up was 100% complete.

Statistical methods

 Coronary event rates were expressed per 100,000 persons per year and age standardized according to the direct method, using 5-year age groups and the European standard population. The annual population counts for the denominators were obtained from the National Population Information System, which is updated continuously. The 28-day case fatality was age standardized using weights derived from the combined age distribution of MI and stroke patients in the WHO MONICA Project. The trends in event rates and case fatality were determined using log-linear Poisson regression models with the year as an independent variable. The regression coefficient of year multiplied by 100 gives the average annual change in percents. The 95% confidence intervals (CI) of the trend estimates were calculated from the standard error of the regression coefficient.

Correction of the trend estimates for the effect of troponins is based on 4359 MI events in the FINAMI areas, with simultaneous determination of troponins and the ‘old’ enzymatic markers of myocardial injury. This material has been described in detail previously. The ratio of the number of MIs diagnosed with enzymatic markers to the number of MIs diagnosed with troponins was taken as the correction coefficient. For simplicity, we used only the ‘old’ cardiac enzymes in this comparison and excluded from the calculation of correction coefficients the cases where the only biomarker of myocardial injury was creatine kinase (CK)-MB mass (n = 542). Events diagnosed using troponins were then weighted with this correction coefficient in the calculation of incidence and attack rates and their trend estimates. Similar procedures were applied for case fatality. As the correction coefficients were derived from cases where the patient had been hospitalized alive and survived at least 1 day, they were applied in the present study on similar cases only. The correction was not considered for mortality trends because of the fact that most of the mortality occurs out of the hospital or in the emergency room.

The 95% CI of the corrected trend estimate had to be expanded for the standard error of the correction coefficient. The 95% CIs for the correction coefficients were calculated using the Taylor approximation from the sampling variations of three groups of events: (a) those diagnosed with troponin only, (b) those diagnosed using enzymatic markers only, and (c) those diagnosed using both troponin and enzymes. Trends were then estimated both at the lower and upper ends of the CI of the correction coefficient. These allowed the estimation of the standard error of the effect of the correction coefficient on the trend. Assuming normality and independence between the regression coefficient used as the trend estimate and the effect of the correction coefficient, the final CI of the corrected trend estimate was calculated from the standard errors of these two. Troponins were adopted between 1997 and 2000 in different hospitals of the FINAMI areas. Accordingly, the starting time of the corrections explained earlier was hospital-specific. The statistical analyses were carried out using SAS.

Results

Altogether, 14,782 coronary events were registered during the study period. Their distribution by sex, age group, and event type is presented in Table 1.

Age- and sex-specific correction coefficients for the effects of troponins are presented in Table 2. The coefficients for the incidence and attack rate are all below one, indicating that correction for the effects of troponins reduced the incidence and attack rate estimates. This effect tended to be stronger in women than in men and in older than in younger individuals and a particularly strong
effect was seen in women aged ≥75. For case fatality, the effect was more inconsistent than for the incidence and attack rate. For 2–28-day case fatality of hospitalized events, the correction coefficient was about one in both men and women aged 35–74. Among persons aged ≥75, the coefficients were clearly more than one. For 29–365-day case fatality, the coefficients were consistently less than one for both age groups among men, indicating that correction for the troponin effect reduced 29–365-day case fatality. Among women, however, the coefficient for the age group ≥75 years was close to one.

During the study period, coronary heart disease mortality in the FINAMI areas decreased 5.3% per year among men and 4.0% per year among women aged 35–74 (Table 3, Supplementary material online, Figure S1). In the age group ≥75 years, a significant decline of 2.3% per year was observed in men, but in women, the change was a non-significant −0.3% per year (Table 3, Supplementary material online, Figure S1).

The incidence of first MI events declined significantly by 2.0% per year in men aged 35–74 (Figure 1, Table 3). After correcting for the effect of troponins, this decline steepened to 2.7% per year. Among women of the same age group, the crude decline was a non-significant 1.0% per year, but after correcting for the effect of troponins, the significant increase changed to a significant decline of 2.7% per year and became statistically significant (Figure 1, Table 3). In the age group ≥75 years, the uncorrected incidence trends were flat both in men and women (−0.2 and 0.3% per year, respectively, Table 3, Supplementary material online, Figure S1). After correcting for the effect of troponins, the decline steepened to 2.0% per year among men and to 1.3% per year among women, but remained non-significant (Table 3).

The attack rate of all MI events declined during the study period on average 3.1% per year among men and 1.9% per year among women aged 35–74 (Table 3, Supplementary material online, Figure S1). After correcting for the effect of troponins, these declines changed to 3.9% per year among men and 3.8% per year among women (Table 3). In the age group ≥75, the attack rate trends were flat in both men and women (Table 3, Supplementary material online, Figure S1). After correcting for the effect of troponins, the flat crude trend changed to a significant decline of 1.9% per year among women (Table 3). Among men, the decline steepened to 1.7% per year but remained marginally non-significant (Table 3). The attack rate of hospitalized MIs (i.e. excluding out-of-hospital deaths and deaths during the first day) declined significantly 1.8% per year among men and 1.8% per year among women aged 35–74 (Figure 2, Table 3). When corrected for the effects of troponins, the declines steepened to 3.0% per year in men and 4.2% per year in women. In persons aged ≥75, a significant increase of 2.9% per year was observed in men and a non-significant increase of 0.8% per year in women (Table 3). After correcting for the effect of troponins, the significant increase became flat 0.3% per year in men, whereas among women, the non-significant increase changed to a significant decrease of 3.6% per year (Table 3).

The 28-day case fatality of MI events declined significantly 2.4% per year among men aged 35–74 (Table 3, Supplementary material online, Figure S2). Among women, the decline was a non-significant 1.2% per year. When corrected for the effect of troponins, the case fatality decline did not change at all among men and only very little among women (Table 3). In the age group ≥75 years, the decline in the 28-day case fatality was significant in men, 2.8% per year, but non-significant among women, 1.0% per year (Table 3, Supplementary material online, Figure S2). Correction for the effect of troponins changed the decline to a non-significant 1.8% per year among men (Table 3). Among women, correction for the effect of troponins made again very little difference in the trend estimate of 28-day case fatality.

Among patients hospitalized alive, the 28-day case fatality declined 3.3% per year in men and 4.9% per year in women aged 35–74 (Table 3). After correcting for the effect of troponins, these trend estimates changed very little. In the elderly patients hospitalized alive, the 28-day case fatality declined a non-significant 2.9% per year among men and a significant 3.7% per year among women (Table 3). After correcting for the effect of troponins, these declines changed to a non-significant 1.3% per year in men and 1.5% per year in women.

The 1-year case fatality for 28-day survivors of MI did not change significantly in any of the four age-sex groups.
patients aged 35–74. In older individuals, the corrected fatality of hospitalized cases declined in both sexes among men, but not in women. The incidence of first MI events among persons aged 35–74 has declined in both sexes, although among women, the decline was hidden by the effect of troponins. In older individuals, no decline was observed in the incidence. The total 28-day case fatality declined in men but not in women, whereas the 28-day fatality of hospitalized cases declined in both sexes among patients aged 35–74. In older individuals, the corrected decline was not significant in either sex. In general, the case fatality trends changed very little after correcting for the effect of troponins. The correction coefficients for 29–365-day case fatality were, however, substantially less than one, but the small number of deaths after day 28 made the CIs of the trend estimates wide.

Table 3  Trends (percentage per year, 95% CI) in coronary events by sex and age group, with and without corrections for the effect of troponins

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Age group</th>
<th>Uncorrected</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35–74 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Men</td>
<td>−5.3 (−6.6, −3.9)</td>
<td>−2.3 (−4.4, −0.1)</td>
</tr>
<tr>
<td>Incidence</td>
<td>Men</td>
<td>−2.0 (−3.0, −0.9)</td>
<td>−0.2 (−2.5, 2.1)</td>
</tr>
<tr>
<td>Attack rate</td>
<td>Men</td>
<td>−3.1 (−4.0, −2.2)</td>
<td>0.2 (−1.5, 1.9)</td>
</tr>
<tr>
<td>Hospitalized attack rate</td>
<td>Men</td>
<td>−1.8 (−2.9, −0.8)</td>
<td>2.9 (0.8, 5.1)</td>
</tr>
<tr>
<td>28-day case fatality</td>
<td>Men</td>
<td>−2.4 (−3.8, −1.0)</td>
<td>−2.8 (−5.0, −0.5)</td>
</tr>
<tr>
<td>2–28-day case fatality of hospitalized events</td>
<td>Men</td>
<td>−3.3 (−5.9, −0.7)</td>
<td>−2.9 (−6.2, 0.4)</td>
</tr>
<tr>
<td>29–365-day case fatality</td>
<td>Men</td>
<td>4.4 (−0.1, 8.8)</td>
<td>1.4 (−4.3, 7.1)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>−4.0 (−6.3, −1.8)</td>
<td>0.9 (−0.7, 2.4)</td>
</tr>
<tr>
<td>Mortality</td>
<td>Women</td>
<td>−1.0 (−2.7, 0.6)</td>
<td>−0.3 (−1.9, 1.3)</td>
</tr>
<tr>
<td>Incidence</td>
<td>Women</td>
<td>−1.9 (−3.3, −0.6)</td>
<td>0.8 (−0.4, 2.1)</td>
</tr>
<tr>
<td>Attack rate</td>
<td>Women</td>
<td>−1.8 (−3.4, −0.2)</td>
<td>0.8 (−0.8, 2.3)</td>
</tr>
<tr>
<td>Hospitalized attack rate</td>
<td>Women</td>
<td>−1.2 (−3.5, 1.1)</td>
<td>−1.0 (−2.6, 0.7)</td>
</tr>
<tr>
<td>28-day case fatality</td>
<td>Women</td>
<td>−4.9 (−8.5, −1.2)</td>
<td>−3.7 (−6.1, −1.3)</td>
</tr>
<tr>
<td>2–28-day case fatality of hospitalized events</td>
<td>Women</td>
<td>−3.2 (−9.0, 2.6)</td>
<td>−7.6 (−15.7, 0.5)</td>
</tr>
<tr>
<td>29–365-day case fatality</td>
<td>Women</td>
<td>−3.0 (−6.3, 0.1)</td>
<td>−2.4 (−6.7, 1.9)</td>
</tr>
</tbody>
</table>

Discussion

The present study provided some new interesting insights into the coronary heart disease event trends and in the effects of troponins on these trends. The study showed that the decline in coronary mortality has continued in Finland and that it extended to the older age groups in men, but not in women. The incidence of first MI events among persons aged 35–74 has declined in both sexes, although among women, the decline was hidden by the effect of troponins. In older individuals, no decline was observed in the incidence. The total 28-day case fatality declined in men but not in women, whereas the 28-day fatality of hospitalized cases declined in both sexes among patients aged 35–74. In older individuals, the corrected decline was not significant in either sex. In general, the case fatality trends changed very little after correcting for the effect of troponins. The correction coefficients for 29–365-day case fatality were, however, substantially less than one, but the small number of deaths after day 28 made the CIs of the trend estimates wide.

The effects of biomarkers in other studies

The importance of consistent criteria for the monitoring of MI events has been emphasized repeatedly, for example, in the 1980s, after the adoption of CK-MB isoenzyme, which also was more sensitive and specific than the earlier markers of myocardial injury. The effect of troponins on trends in coronary events. In the incidence and attack rate, our data showed that the effect of troponins was stronger in women than in men and stronger in older than in younger individuals. Other investigators have reported 26–58% more MIs with troponins than with enzymatic markers. The scale reflects differences in patient characteristics, assays used, and diagnostic criteria for the MI events included in the comparisons. No study has published age- and sex-specific numbers so far.

Case fatality and prognosis

The effect of troponins on case fatality trends was smaller and more inconsistent than their effect on incidence and attack rate. The fact that the 28-day case fatality decline changed only very little after correcting for troponins was to some extent surprising. As troponins detect smaller MIs, one might assume them to lower the case fatality. We have, however, recently shown that the additional MI cases, revealed by the use of troponins, have poor prognosis, which was probably because of their unstable coronary situation. Another large study from Canada has also documented that elevated troponin is a marker of poor 1-year prognosis among patients with acute coronary syndrome. Most other studies on the effect of troponins on case fatality have been conflicting or inconclusive, probably because of the small number of deaths after day 28 (Table 3).
because of their small size and heterogeneity of patient populations.1–4,13

Coronary event trends in the elderly

There is very little population-based data on trends in coronary events among the elderly, except for the routine mortality statistics. In the 1970s and 1980s, the decline in coronary mortality started from the younger age groups and then later spread to middle-aged individuals.15 Against this background, it was interesting to note that now the coronary mortality is declining also among men aged ≥75 in Finland. Correction for the effect of troponins revealed that also the attack rate of coronary events was declining among the elderly, particularly among women. Community surveillance projects also elsewhere have started to collect data on MI events in the elderly,16,17 but very little trend data in persons aged ≥75 have been published so far. The importance of the elderly age groups is underscored by the fact that in 2002, the mean age of having the first MI in Finland was 70.2 years among men and 80.0 years among women.18

Strengths and limitations

A strength of our article is that it is a large population-based study covering all MI events in the populations of monitored areas irrespective of the age of the patient. Furthermore, we could base our assessment of troponin effects on over 4000 MIs, with simultaneous determination of cardiac troponins and enzymes. The correction coefficients derived from this material are fairly general in nature, as the material has been collected in the usual health care setting from several hospitals using different troponin kits. Nevertheless, our coefficients should be applied to other materials only with caution because the effects of troponins may depend on the case mix of the patients, treatments and invasive procedures administered, and several other factors. Another limitation is that we have compared troponins with the ‘old’ cardiac enzymes, excluding CK-MB mass from the calculation of correction coefficients. CK-MB mass is also more sensitive and specific than CK-MB isoenzyme. Therefore, the effect of troponins would be smaller when compared with the results based on CK-MB mass determinations.

Conclusions

Declining trends in the incidence and attack rate of MI events in Finland during 1993–2002 were partly hidden by the effect of troponins, especially among women. Considerable declines were seen also in the 2–28-day case fatality of patients hospitalized alive. Declines in incidence, attack rate, and case fatality have all contributed to the considerable declines in coronary mortality, which extended to the older age groups among men.
Supplementary material

Supplementary material is available at European Heart Journal online.

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Conflict of interest: none declared.

Appendix: Investigators of the FINAMI Study Group


References