SUPPLEMENTAL MATERIALS

Supplemental Methods

A method for adjusting population hospitalized myocardial infarction event rates for dynamic changes in cardiac biomarkers over time in community surveillance

A technical report prepared by the Atherosclerosis Risk in Communities (ARIC) Study Coordinating Center

INTRODUCTION

Immunoassays for troponin (I and T) that serve as biomarkers for myocardial damage were developed in the late 1980's. These cardiac muscle structure proteins have high cardiospecificity and high sensitivity for minor myocardial damage, and have a long diagnostic time-window.

The surveillance component of the Atherosclerosis Risk in Communities (ARIC) Study evaluates time trends in hospitalized MI in four U.S. communities. Since its beginning in 1987 it has used standardized criteria based upon symptoms (cardiac pain), electrocardiographic evidence and biomarker levels to classify eligible events as definite, probable, suspect or no MI. In the early period (1987-1995) cardiac biomarkers monitored included total creatine kinase (Total CK) and its myocardial fraction (CK-MB), lactate dehydrogenase (LDH) and its subfractions. Data on troponin measurements were monitored beginning in 1996.

Stemming from their greater sensitivity and specificity than other cardiac biomarkers, the introduction of troponins in diagnostic protocols complicates the epidemiologic interpretation of time trends in hospitalized MI. A larger number of MIs observed in recent years could be an artifact due to more events with minor myocardial damage being classified as MI using troponin. Thus, MI rates would not be comparable with rates in the earlier period. Even before troponin was introduced, changes in biomarker usage could have affected the observed number of MIs because CK-MB has a higher sensitivity and specificity for the diagnosis of acute MI than total CK and LDH and its subfractions.

The joint statement by the European Society of Cardiology and the American College of Cardiology on the redefinition of myocardial infarction emphasized that continued tracking of the burden and occurrence of coronary events in the community will require innovative methods for adjusting the new criteria to the old. To permit a meaningful epidemiologic interpretation of the trends in MI, we outline here a new application of an existing method that "standardizes" the rates to a consistent usage of biomarkers.

METHODS

Study Population

ARIC community surveillance monitors admissions to acute care hospitals and deaths due to coronary heart disease (CHD) among all residents aged 35-74 in four communities: Forsyth County, North Carolina; Jackson, Mississippi; eight northern suburbs of Minneapolis, Minnesota; and Washington County, Maryland.

Data on Hospitalization for Myocardial Infarction

Eligibility for hospital surveillance was based on age, residence and discharge diagnosis (International Classification of Diseases Clinical Modification (ICD9-CM) codes 402, 410-414, 427-428 and 518.4). Eligible hospitalizations were sampled based on date of discharge. Selected medical information was abstracted from the medical records by certified abstractors including all pertinent cardiac biomarker levels within the first 4 days of hospital admission. Up to three electrocardiograms (ECG) were sent to the University of Minnesota ECG Reading Center for classification according to the Minnesota Code. Cardiac biomarkers monitored in 1987-95 included total CK, CK-MB, LDH and its sub-fractions. Values of cardiac troponins have been recorded from 1996 to present. Among hospitalizations with some biomarkers measured, 8%, 73%, 88%, 97%, 98% and 98% included troponin in years 1996-2001, respectively. Individual biomarkers were classified as normal, incomplete, equivocal and abnormally elevated. Abnormally elevated biomarkers were defined as at least 2 times of upper limit of normal whereas an equivocal elevation was defined as between 1 and 2 times of upper limit of normal. Abnormally elevated biomarkers were downgraded to equivocal when thought to be spurious (e.g. due to trauma).

MI was classified as definite, probable, suspect, or no MI based upon published criteria [that] have been consistent since 1987. Events classified by a computerized algorithm as either definite or probable MI were considered to be MI for this analysis (Table 1).

Statistical Analysis

In this method we adjusted rates of MI for changes in biomarkers by imputing the number of MIs that would have occurred in a pre-troponin year (i.e. had troponin not been introduced and other biomarkers not dropped), and had the distribution (i.e. relative frequencies) of the biomarker usage combinations been the same across years. The adjustment included two imputation and one standardization procedures, (1) imputing the distribution of the pre-troponin combinations

(PTC, the biomarker usage combinations that would have occurred in a pre-troponin year), (2) imputing the probability of MIs in each of the PTC, and (3) standardizing the imputed probability of MIs (and hence the number of MIs) to the distribution of the PTC in a reference period mimicking direct adjustment. This method can be viewed as an “extended” direct adjustment method where the distribution of the PTC for post-1995 events had to be imputed, from which the probability of MIs in each of the PTC could be estimated by data with overlaps in troponin use and other biomarkers, and finally the PTC-specific probability of MIs was weighted by the distribution of the PTC in the reference period.

This adjustment method did not change the rate of MI in the reference year, but changed the rates in other pre-troponin years due to the standardization of the biomarker distributions. It also changed the rates in the troponin years due to the imputation of PTC and the standardization of their distributions.

Note that the adjustment procedures (for both the imputation and standardization) were performed pain and ECG category-specific since (1) the probability of MI differed in different pain-ECG categories (which were related to the severity of MI), and (2) three out of the six pain-ECG categories did not need an imputation because pain and ECG alone determined the MI classification (Table 1). They were also age- and event year-specific so that the age-adjusted rate of MIs in the reference year remained the same before and after adjustment. In addition, the adjustment accounted for the number of biomarkers used but not the total number of samples tested.

Using the ARIC data in 1987-1995 we identified three PTC: “CK-MB (with or without CK/LDH)”, “CK/LDH alone”, and “NONE” (no biomarkers). The first combination included events used CK-MB and one or more of the total CK, LDH and its sub-fractions (denoted as CK/LDH). A handful of events that used CK-MB alone were also included in this combination. We chose 1995, the year just before troponin was introduced, as the reference period for the standardization in biomarker usage distribution.

I. Adjustment for events in pre-troponin years

For events in the pre-troponin years the distribution of the PTC and the number of MIs remain was standardized without imputation. Since the distribution of the PTC were not the same across pre-troponin years (1987-95), and since this variation could affect MI frequency, the

probability of MIs in each of the pre-troponin years was standardized to the distribution of the PTC in 1995 (the reference period) mimicking the direct adjustment method. The adjusted probability of MIs was the weighted sum of the probability of MIs (the observed proportion of MIs) in each of the PTC weighted by the relative frequencies of the PTC in 1995. The adjusted number of MIs was simply the total number of events times this adjusted probability. The adjustment was age group- and pain-ECG category specific and was applied only to pain-ECG categories needing adjustment.

Next, we summed up the adjusted number of MIs over all pain-ECG categories needing adjustment plus the observed number of MIs over the other pain-ECG categories not needing adjustment to get the final number of MIs. The adjusted rate of MI was the final number of MIs divided by the population size. We followed the same procedures for events in age-specific groups to compute age-specific rates, and then directly adjusted these rates to the age distribution in the US 2000 population to obtain the age-adjusted rates of MI adjusted for changes in biomarkers.

II. Adjustment for events in troponin years

Adjustment of rates of MIs in troponin years (post 1995) is more complicated. It is insufficient to simply ignore troponin values and then perform direct adjustment, because other biomarkers may have been dropped. Rather, we imputed relative frequencies of the PTC for post-1995 events in various troponin/biomarker combinations under the counterfactual assumption that troponin had not been introduced and other biomarkers not replaced. We then imputed the probability of MI in each of the imputed PTC using (1) the observed biomarker and troponin values and (2) the observed proportions of MI under pre-troponin rules from years of overlap in troponin use with CK-MB, CK/LDH use (1997-2001). Lastly, we mimicked direct adjustment to standardize the probability of MIs. Imputation procedures for post-1995 events in pain-ECG categories needing adjustment are described in detail below.

<u>Imputation of the distribution of the PTC</u>

We used the following assumptions to impute the PTC for post-1995 events. (1) If in troponin years CK-MB or CK/LDH were used, then the same type of biomarkers would have been used and the biomarker classification would remain the same. (2) If no biomarkers were used in troponin years, then no biomarkers would have been used in pre-troponin years. (3) If troponin was used in post-1995, at least one of the CK-MB and CK/LDH would have been used in the

pre-troponin years when troponin was not available, and the imputed pre-troponin biomarker classification would be either positive or negative if not used in post-1995. We used “positive” biomarker to represent a biomarker classification that would classify an event as an MI whereas “negative” is for the classification determining an event to not be an MI.

We imputed the relative frequencies of the PTC as the proportion of the PTC in the reference period conditional on the possible imputed combinations (Table 2).

Imputation of the probability of MIs

For post-1995 events, the MI was imputed under the following rules: (1) if either CK-MB or CK/LDH was positive (regardless of troponin values) then the events were MIs; (2) if troponin was used and one or both of the CK-MB and CK/LDH was not used and none of the CK-MB and CK/LDH was positive, then we used events in 1997-2001 to impute the probability of MIs (described below); and (3) in all other cases, events were not MIs.

For events under each of the 27 combinations of troponin*CK-MB*CK/LDH with respect to their biomarker classification (being positive, negative or missing), the imputed probability of MIs was 1 for those under rule #1, and 0 for rule #3. For events under rule #2, the probability of MIs (detail formula in Table 2) was imputed as the proportion of the imputed events with positive CK-MB or positive CK/LDH, and we used 1997-2001 data to estimate this proportion. The corresponding imputed number of MIs in a troponin*CK-MB*CK/LDH combination in each of the PTC was the number of the events in the combination (N_i, i for the troponin*CK-MB*CK/LDH combinations) times the relative frequency (f_{ij}, j for the 3 PTC) of the PTC times the imputed probability (p_{ij}) of MIs.

Next, we summed up the imputed number of MIs over all 27 troponin*CK-MB*CK/LDH combinations and divided by the overall imputed number of the events in that PTC (which was the sum of $N_i \times f_{ij}$ over all 27 combinations) to get the overall probability of MIs in each of the PTC.

Procedures to standardize the PTC-specific probability of MIs and to compute the final adjusted number of MI and the age-adjusted rates were as outlined earlier for events in the pre-troponin years and therefore not repeated here.

An example for the imputation

Suppose there were N_i events in a post-1995 year that were in pain-ECG category A, age 35-54 with negative troponin, missing CK-MB and negative CK/LDH, (-, M, -) in the notation of Table 2. We assume that in the reference year 57.6% used CK-MB (with or without CK/LDH), 34.1% used CK/LDH alone, and 8.3% no biomarkers (Table 4). Furthermore, we assume that out of the 2141 events in the post-1995 period with (- troponin, ± CM-MB, - CK/LDH) in pain-ECG category A, 6.5% had positive CK-MB, the (-, ±, -) combination in Table 5.

We first determined that events in (-, M, -) combination were imputed as "CKMB (with or without CK/LDH)" or "CK/LDH alone" for their PTC. (It was impossible to impute (-,M,-) events as "NONE" because CK/LDH was used and was negative). Next, we imputed the same percentages of events to the PTC as in the reference period conditional on the possible imputed PTC, that is, 57.6/(57.6+34.1)=62.8% of the N_i events were imputed as "CKMB (with or without CK/LDH)" and the possible classification combinations were (± CM-MB, - CK/LDH). The remaining 37.2% were imputed as "CK/LDH alone" with only one classification combination (missing CK-MB, - CK/LDH) should these events have occurred in the reference year.

For post-1995 events in (-, M, -) to be an MI under pre-troponin years we must have CK-MB positive since CK/LDH was negative. Thus in the PTC of "CK-MB (with or without CK/LDH)" we imputed the number of MIs by $N_i \times 62.8\% \times 6.5\%$, which is simply the number of the imputed events in this PTC (i.e. $N_i \times 62.8\%$) times the imputed probability of MIs (6.5%). We imputed zero MIs in the PTC of "CK/LDH alone" since CK/LDH was negative and CK-MB missing for all events imputed to this PTC. Note that for all events in pain-ECG categories needing adjustment, no MIs would be imputed from the PTC of "NONE".

For purposes of comparison, the incident rates of MIs (age-adjusted to the US 2000 population) were computed by 4 approaches: M1) fully adjusted, as described above, M2) partially adjusted: imputed PTC and imputed number of MIs, but the distributions of the PTC were not standardized, M3) observed rates (using ARIC MI algorithm) including troponin (when available), and M4) observed rates excluding troponin. The last two approaches did not have any adjustment.

The estimated number of MIs from the fully adjusted method (M1) and the observed using troponin (M3) were fitted via Poisson regression models to estimate the annual percent change in the rates of MI. The corresponding confidence intervals were estimated by bootstrapping with 500 replications.

Since eligible events were sampled, all analyses were weighted by the inverse of the sampling fractions except for the Poisson regression models where the weighted number of MIs was the response variable. All of the computations were performed in SAS version 8.0.

APPLICATION

Table 3 presents the biomarker distribution for events needing adjustment (i.e. in pain-ECG categories A, B and C in the notation of Table 1). Overall, there was a clear trend of increased use of CK-MB and CK/LDH together and decreased use of CK/LDH alone between 1987 and 1995 (pre-troponin years). Counts of CK/LDH may overstate their actual use for MI diagnosis, because they may be measured routinely in a non-MI admission battery. Among events needing adjustment, few (8%) used troponin in 1996 but usage increased to 93% in 2001. (Among hospitalizations with some biomarkers measured, 98% used troponins in 2001). In the troponin years (1997-2001) 53-69% had all three types of biomarkers (CK-MB, CK/LDH and troponin) measured together, 20-24% used both CK/LDH and troponin, and very few used troponin alone (up to 3%). Four to 8% of the events under consideration had no biomarkers measured each year, given the broad range of ICD codes screened. Similar trends were observed for gender-specific distributions (data not shown).

Table 4 shows the age-specific distribution of the PTC in the reference year (1995) for pain and ECG categories needing adjustment. These were the “standard” distributions for the direct adjustment. The most severe events (with evolving or diagnostic ECG and cardiac pain) tended to have more types of biomarkers measured, and all of them had at least one type of biomarkers measured in the reference year.

As an example, table 5 shows the observed percentage of MIs (by CK-MB and/or CK/LDH being positive) in 1997-2001 for various troponin/biomarker combinations where troponin was used and neither CK-MB nor CK/LDH was positive and one or both of the CK-MB and CK/LDH was missing. For example, of the 432 events in pain-ECG category A that had positive troponin

and available CK-MB , i.e., the (+, ±, A) combination, 63.7% had MI based on CK-MB or CK/LDH being positive. Thus, we estimate that 63.7% of the events with positive troponin, missing CK-MB and missing CK/LDH would have been MI should these events have had CK-MB measured but not troponin. As expected, the most severe events (category C) had a higher chance of being classified as an MI under pre-troponin rules compared to events in the other pain-ECG categories. Furthermore, events with positive troponin and available CK-MB had the highest chance of being classified as an MI (63-89%), and events with negative or missing CK-MB had the smallest chance. Similar results were observed in age-specific groups and in estimations limited to using incident events only (both data not shown). For stability the proportion of MIs using all eligible events needing adjustment from the overall age group were used to impute the number of incident MIs.

The annual percentage change of the age-adjusted rates of incident MI, with and without adjustment for changes in biomarkers, is shown in Table 6. Without adjustment (including troponin), the rates changed little over years. With adjustment, the rates declined 2.7% (95% CI: 1.8, 3.6) annually in men, 3.4% (95% CI: 2.2, 4.6) in women and 2.9% (95% CI: 2.3, 3.6) overall.

DISCUSSION

In order for epidemiologists to distinguish real change from artifact in interpreting time trends in rates of MI in the community, the classification of MI needs to be stable. Because measurements of troponin were introduced in community hospitals, we sought to create comparability by adjusting the rates (trends) of MI in the troponin years to remove the troponin effect. Our fully adjusted method imputed the number of MIs adjusting for the biomarker usage combinations and their distributions, and therefore provided a meaningful interpretation for the trend of MI beginning with pre-troponin rates and extending into the post-troponin era.
Our adjustment method mainly extended the well-known direct adjustment to impute the standardized biomarker combinations and to standardize their distributions across study years.

We expected that the rates of MI in the early study period in ARIC (1987-1994) would have been higher than the observed if the biomarker distributions had been the same as in the reference year (1995), because fewer types of and less sensitive biomarkers were used in that

period (Table 3). Our results supported this expectation and justified the necessity of adjusting the trends for biomarker distributions even before troponins were introduced.

Our results also show that events with positive troponin or with more severe pain-ECG findings had a larger chance being classified as MI (Table 5). The only exception was when troponin was positive and CK-MB was negative, as the only chance these events would be classified as MI was having positive CK/LDH, yet CK/LDH have lower sensitivity in detecting MI. These results are consistent with the expectations.

The partially adjusted method imputed PTC for events in troponin years but did not standardize biomarker distributions or numbers of biomarkers used. Therefore, the imputed numbers of MI from this method were bounded above by the observed number including troponin, and bounded below by the observed number excluding troponin.

Since troponin is more sensitive and specific in detecting MI, it may eventually replace the use of other biomarkers, which has already occurred in a few individual hospitals. Although there was an increase use of troponin in the ARIC hospitals (73% usage in 1997 and 98% in 2001 among hospitalizations with some biomarkers measured), we have not yet observed widespread adoption of troponin without retention of other biomarkers. For this reason the fully adjusted rates did not differ much from the observed excluding troponin in the post-1995 period. If ARIC hospitals completely switch to troponin only, our fully adjusted method would then be quite different from the observed excluding troponin, and adjustment would be essential to meaningfully interpret the trend in MI rates.

We selected a pre-troponin year (1995) as the reference year for standardization. Although the rates of MI will differ if the reference period were chosen differently, the annual percent change was invariant to the choice of the reference period. If one chose a troponin year, say, 2001, as the reference year, the biomarker combinations in the troponin years would need to be imputed for pre-troponin events. This approach is more complicated than the one we have shown as there are more biomarker combinations in the troponin years. However, it has some attraction as it would show real rates for the most current years.

Our imputation of the number of MIs in each troponin/biomarker combination was based on the percentage of events with positive CK-MB or CK/LDH in 1997-2001. These percentages have

denominators of at least 100 and mostly above 400 (Table 5), and hence should be quite stable. We did not use gender-specific or other subgroup specific percentages as the sample sizes became small. Although the current method was applied to age-adjusted incident rates of MI, extensions to recurrence and attack rates and other types of events are straightforward.

Table 1. ARIC criteria for classifying hospitalized definite or probable MI

Cardiac Pain	ECG Finding	Biomarker Classification	MI Diagnosis	Pain-ECG Category*
Present	Evolving Diagnostic	Any	MI	D
	Evolving or Diagnostic	Equivocal or Abnormal (+)	MI	C
		Incomplete or Normal (-)	No-MI	C
	Equivocal or uncodable (including normal)	Abnormal (+)	MI	B
		Incomplete, Normal or Equivocal (-)	No-MI	B
Absent	Evolving Diagnostic	Any	MI	D
	Evolving or Diagnostic	Abnormal (+)	MI	A
		Incomplete, Normal or Equivocal (-)	No-MI	A
	Equivocal or uncodable (including normal)	Any	No-MI	D

* Pain-ECG categories A, B and C need adjustment for time trends in biomarkers. MI diagnosis for pain-ECG category D does not depend upon biomarker classification, and therefore does not need adjustment.

Table 2. Imputed relative frequency of the pre-troponin combinations (PTC) and the imputed probability of MIs under various troponin/biomarker combinations.

	Imputed Relative Frequency		Imputed Probability of MIs	
Troponin/biomarker combination* (troponin, CK-MB, CK/LDH)	CK-MB (with or without CK/LDH)	CK/LDH alone	CK-MB (with or without CK/LDH)	CK/LDH alone
(A,+,+)	1	0	1	0
(A,+,-)	1	0	1	0
(A,-,+)	1	0	1	0
(A,-,-)	1	0	0	0
(A,+,M)	1	0	1	0
(+,-,M)	1	0	$\frac{N(+,-,+)}{N(+,-,A)}$ ♦	0
(-,-,M)	1	0	$\frac{N(-,-,+)}{N(-,-,A)}$	0
(M,-,M)	1	0	0	0
(±,M,+)	$\frac{r_1}{r_1+r_2}$ **	$\frac{r_2}{r_1+r_2}$	1	1
(M,M,+)	0	1	0	1
(+,M,-)	$\frac{r_1}{r_1+r_2}$	$\frac{r_2}{r_1+r_2}$	$\frac{N(+,+,-)}{N(+,\pm,-)}$	0
(-,M,-)	$\frac{r_1}{r_1+r_2}$	$\frac{r_2}{r_1+r_2}$	$\frac{N(-,+,-)}{N(-,\pm,-)}$	0
(M,M,-)	0	1	0	0
(+,M,M)	$\frac{r_1}{r_1+r_2}$	$\frac{r_2}{r_1+r_2}$	$\frac{N(+,+,A)+N(+,-,+)}{N(+,\pm,A)}$	$\frac{N(+,M,+)}{N(+,M,\pm)}$
(-,M,M)	$\frac{r_1}{r_1+r_2}$	$\frac{r_2}{r_1+r_2}$	$\frac{N(-,+,A)+N(-,-,+)}{N(-,\pm,A)}$	$\frac{N(-,M,+)}{N(-,M,\pm)}$
(M,M,M)▲	0	0	0	0

* Value A is for any biomarker classification, + for positive, - for negative and M for missing biomarkers (not used).

** r_1, r_2 and r_3 ($r_1 + r_2 + r_3 = 1$) represent the relative frequency with respect to PTC "CK-MB", "CK/LDH" and "NONE" in the reference year, respectively.

♦ $N(X, Y, Z)$ represents the number of events in 1997-2001 in combination (X, Y, Z) with respect to the classification of (troponin, CK-MB, CK/LDH).

▲ Events in combination (M,M,M) were all imputed as "NONE" (no biomarkers), and none of them would be imputed as an MI.

Table 3. Biomarker distribution among events in which biomarkers determined MI diagnosis in 1987-2001

Year	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Events (N)	4075	4174	4071	4138	4169	3916	4284	4329	4309	4406	4309	4404	3691	4004	4031
Biomarker Usage (%)															
CK-MB+CK/LDH* only	51.4	53.9	53.6	56.0	53.6	59.0	59.8	68.9	69.0	65.2	14.4	7.6	0.9	0.5	0.4
CK/LDH only**	40.3	40.5	40.8	38.3	40.0	35.4	35.8	27.2	26.4	21.3	5.8	2.2	1.0	0.4	0.4
No biomarkers	8.3	5.6	5.6	5.8	6.4	5.6	4.3	3.9	4.6	5.7	7.0	7.8	8.2	7.1	5.8
Troponin only										0.0	0.1	1.1	1.6	3.2	2.5
CK/LDH + Troponin										1.5	19.7	20.1	23.5	23.8	21.7
CK-MB + CK/LDH + Troponin#										6.2	52.9	61.1	64.7	65.0	69.2

* Includes a handful of events with CK-MB alone.

** Counts of CK/LDH, especially in the latter years, may overstate their actual use for MI diagnosis, because they may be measured routinely in a non-MI admission battery.

Includes a few events (less than 2%) using troponin and CK-MB but without CK/LDH.

Table 4. Distribution of the pre-troponin combinations (PTC) in the reference year (1995) in pain-ECG categories needing adjustment, by age group.

			PTC		
Pain-ECG category	Age	No. of events	CK-MB **	CK/LDH	None
A	35-54	138	57.6	34.1	8.3
	55-64	185	50.3	36.5	13.2
	65-74	264	57.1	29.3	13.6
B	35-54	359	69.2	26.0	4.9
	55-64	347	80.3	18.2	1.5
	65-74	578	71.0	24.5	4.5
C	35-54	243	92.9	7.1	0.0
	55-64	243	83.2	16.8	0.0
	65-74	336	78.4	21.6	0.0

Pain-ECG Category:
(A) evolving or diagnostic ECG without cardiac pain,
(B) equivocal, normal or uncodable ECG with cardiac pain
(C) evolving or diagnostic ECG with cardiac pain.

** Using CK-MB, with or without CK/LDH.

Table 5. Observed percentage of MIs* in 1997-2001 without using troponin in various troponin/biomarker combinations by pain-ECG category

Troponin/biomarker (troponin, CK-MB, CK/LDH)	Pain-ECG Category **					
	A		B		C	
	% MI	(N)	% MI	(N)	% MI	(N)
(+,±,A)	63.7	(432)	71.9	(1093)	89.4	(2459)
(+,±,-)	62.6	(400)	71.4	(1050)	74.1	(1001)
(-,±,A)	7.6	(2246)	5.3	(4596)	29.0	(1939)
(-,±,-)	6.5	(2141)	4.9	(4429)	16.2	(1588)
(+,-,A)	4.4	(164)	1.0	(310)	13.0	(299)
(-,-,A)	0.9	(2094)	0.4	(4369)	9.9	(1530)
(+,M,±)	0.0	(102)	0.6	(212)	36.9	(519)
(-,M,±)	0.6	(884)	0.0	(2014)	1.1	(702)

* Observed percentages of MIs (i.e. CK-MB or CK/LDH being positive) in 1997-2001. These are the imputed probability of MIs when troponin was used and one or both of the CK-MB and CK/LDH was not used and none of the CK-MB and CK/LDH was positive.

** Pain-ECG Category:
A for evolving or diagnostic ECG without cardiac pain,
B for equivocal, normal or uncodable ECG with cardiac pain, and
C for evolving or diagnostic ECG with cardiac pain.

N is the denominator (i.e. number of events with the specified troponin/biomarker combination in 1997-2001) of the percentages.

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Table 6. Annual percent change (%) in the age-adjusted rates of incident MI in 1987-2001 and the corresponding 95% confidence intervals from the observed including troponin and fully adjusted methods

Group	Fully Adjusted (M1)	95 % confidence interval	Observed including Troponin (M3)	95 % confidence interval
Men	-3.4	(-4.6, -2.2)	1.1	(-0.1, 2.3)
Women	-2.7	(-3.6, -1.8)	-0.2	(-1.1, 0.7)
Total	-2.9	(-3.6, -2.3)	0.3	(-0.4, 1.0)