Trends in five-year survival of patients discharged after acute myocardial infarction

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BACKGROUND: It has previously been shown that the increased use of therapeutic intervention may not reduce patient fatality if there is a simultaneous increase in case severity. The present study was designed to extend the relationship between case severity and therapeutic interventions to long-term survival in the same study population.

OBJECTIVE: To compare five-year survival of patients discharged after acute myocardial infarction from 1984 to 1988 and from 1989 to 1993, and to evaluate possible reasons for survival differences.

METHODS: The present study was population-based. Survival time was determined by record linkage into the Canadian Mortality Database. Association of five-year survival with patient characteristics, in-hospital treatment and discharge medications was assessed by logistical regression analysis. Case severity was calculated as the probability of death within five years, given the patient profile and excluding any interventions.

RESULTS: Between the two study periods, most patient characteristics and treatment intensity changed, but case severity for the study population remained constant. Five-year survival improved from 74.8% to 79.2% ($P_{\chi^2}=0.001$). The improvement was adequately described by the combination of changes in patient profile and treatment without residual period effect ($P_{\text{goodness-of-fit}}=0.752$). The treatments significantly associated with five-year survival were coronary artery bypass graft surgery (OR 2.74; 95% CI 1.86 to 4.05), percutaneous coronary intervention (OR 2.63; 95% CI 1.67 to 4.14) and thrombolysis (OR 1.98; 95% CI 1.50 to 2.62) during admission, as well as acetylsalicylic acid (OR 1.39; 95% CI 1.15 to 1.68) or beta-blocker (OR 1.60; 95% CI 1.34 to 1.92) prescription at discharge.

CONCLUSIONS: Changes in patient profile did not affect long-term prognosis; instead, treatment modalities accounted for the observed improvement in five-year survival.

Key Words: Cause of death; Mortality; Myocardial infarction; Record linkage; Survival analysis

Survival is the major outcome measure for studies of acute myocardial infarction (AMI). The follow-up period for these survival studies is most commonly the duration of hospital stay, or sometimes it is one month. Less frequently, survival is documented for a one-year period and, rarer still, five years. A longer follow-up period is important because long-term survival may be subject to different influences than short-term survival. This is suggested by the finding that ST elevation myocardial infarction (MI) and non-ST elevation MI differ more or less significantly in their short-term mortality (1-3)

Les tendances de survie de patients ayant reçu un congé après un infarctus aigu du myocarde au bout de cinq ans

HISTORIQUE : Il a déjà été démontré que l'augmentation des interventions thérapeutiques ne réduit pas toujours le risque de décès lorsque le cas devient concurrentement plus grave. La présente étude a été conçue pour accroître le lien entre la gravité de la maladie associée aux interventions thérapeutiques et la survie à long terme d'une même population à l'étude.

OBJECTIF : Comparer le taux de survie au bout de cinq ans de patients ayant obtenu leur congé après un infarctus aigu du myocarde entre 1984 et 1988 et entre 1989 et 1993, et évaluer les raisons possibles pour expliquer les différences de survie.

MÉTHODOLOGIE : La présente étude était une étude de population. La durée de survie a été établie en reliant les dossiers avec la Base canadienne de données sur la mortalité. L'association entre la survie au bout de cinq ans et les caractéristiques des patients, le traitement pendant l'hospitalisation et les médicaments prescrits au congé a été évaluée au moyen d'une analyse de régression logistique. La gravité des cas a été calculée d'après la probabilité de décès au bout de cinq ans, compte tenu du profil du patient et en excluant toute intervention.

RÉSULTATS : Entre les deux périodes d'étude, la plupart des caractéristiques des patients et l'intensité des traitements ont changé, mais la gravité des cas de la population à l'étude est demeurée constante. La survie au bout de cinq ans est passée de 74,8 % à 79,2 % ($P_{\chi^2}=0,001$). Cette amélioration a été décrite correctement comme la combinaison des changements de profil des patients et de traitement sans effet sur la période résiduelle ($P_{\text{validité de l'ajustement}}=0,752$). Les traitements associés de manière significative à la survie au bout de cinq ans étaient le pontage aortocoronarien (RR 2,74; 95 % IC 1,86 à 4,05), l'intervention coronaire percutanée (RR 2,63; 95 % IC 1,67 à 4,14) et la thrombolyse (RR 1,98; 95 % IC 1,50 à 2,62) pendant l'hospitalisation, de même que la prescription d'acide acétylsalicylique (RR 1,39; 95 % IC 1,15 à 1,68) ou de bêtabloquants (RR 1,60; 95 % IC 1,34 à 1,92) au congé.

CONCLUSIONS : Les modifications au profil des patients n'ont pas eu de conséquences sur le pronostic à long terme. Ce sont plutôt les modalités de traitement qui expliquaient l'amélioration observée de la survie au bout de cinq ans.

but have the same long-term survival (4). A meta-analysis has determined that between the 1960s and the 1980s, the one-month mortality decreased significantly from 31% to 18%, but that five-year mortality did not decline significantly (5). A more recent finding (6) showed that between 1975 and 1995, the in-hospital patient fatality declined consistently but without change in crude long-term survival. However, a decline was noted in one-year fatality during the latter years of the observation period. An opposite finding was reported by a Danish study (7) that analyzed the survival experience of AMI

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patients occurring between 1982 and 1991. No improvement in short-term survival was found, but long-term survival improved for men and not for women. A Scottish study (8) looking at short- and long-term survival trends for AMIs occurring between 1986 and 1995 found a significant decrease in both short- and long-term patient fatality. A Swedish study by Engström et al (9) showed that between 1978 and 1995, the trends in 28-day survival and three-year survival of AMI patients improved markedly. However, the trends were found to be less favourable in socioeconomically deprived areas. A Canadian investigation of patient fatality and one-year mortality after AMI (10) found that both outcome measures decreased significantly between 1994 and 1999. The investigators suggested that the improved survival after AMI may be associated with recent escalation in the use of revascularization and pharmacological therapies.

However, the outcome of AMI was determined not only by therapeutic interventions but also by case severity. We have previously shown (11) that despite a significant increase in the use of therapeutic intervention, patient fatality may not decline if there is a simultaneous increase in case severity (11). The present study was designed to explore the relationship between case severity, therapeutic interventions and long-term survival in the same study population.

METHODS

Study population

Between January 1, 1984, and December 31, 1993, all AMIs occurring in the population of Halifax County (Nova Scotia) in patients 25 to 74 years of age had been entered into the Halifax County Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) database. The details of patient identification and data collection have been previously reported (12). Patients were selected for the present study if they had survived hospitalization and had been diagnosed according to World Health Organization MONICA criteria (13) as definite AMI, possible AMI or ischemic cardiac arrests. For each selected patient, demographics, clinical history (Hx), treatment during hospital stay and discharge medications were extracted from the MONICA database. Variables describing Hx were coded 'yes' or 'no' depending on whether the presence or absence was explicitly mentioned in the patient's chart; otherwise, they were coded 'unknown'.

To avoid selection bias for patients with multiple events during the study period, one event was selected at random as the index event.

Fatal cases were defined as death occurring from any cause. In an earlier study of 28-day patient fatality (11), the authors found that between 1984 and 1988, patient fatality had changed little but a significant decline occurred between 1989 and 1993. For the present study, five-year survival among hospital survivors of AMI occurring from 1984 to 1988 and from 1989 to 1993 was contrasted. The Queen Elizabeth II Health Sciences Centre Research Ethics Committee approved the research.

Record linkage

With the collaboration of Statistics Canada, the Canadian Mortality Database (14) was searched to determine whether any of the study patients had died anywhere in Canada within five years of the date of their AMI. The search used the latest version of record linkage software developed for epidemiological follow-up studies (Generalized Record Linkage System [GRLS.v4], Statistics Canada, Ontario) (15). The method is applicable when no unique

identifier is available for linkage. It is based on a probabilistic approach and computes the probability of a match from a set of nonunique identifiers, weighted according to their discriminating power. Its reliability has been carefully validated in a number of settings (16-19). In the present case, the set of nonunique identifiers consisted of full name, sex, full date of birth, postal code of last known place of residence and an index date. The index date was the date when the AMI had occurred in the particular patient.

Definition of variables

Cause of death was the *International Classification of Diseases, 9th revision* (ICD-9) (20) code for the immediate cause of death as recorded on the death certificate or in the Canadian Mortality Database (14). For the purpose of analysis, the following cause groups were formed:

- MI and other coronary artery diseases (CADs): ICD-9 codes 410 to 414.
- Other vascular disease: ICD-9 codes 401 to 405, 415 to 417, 420 to 459.
- Neoplasm: ICD-9 codes 140 to 239.
- Other: all other ICD-9 codes.

The assessment of left ventricular (LV) impairment was based on clinical features, similar to the Killip classification:

- Mild to moderate required x-ray evidence, increased jugular venous pressure, rales, or presence of the third heart sound (S3).
- Severe LV impairment required pulmonary edema.
- Shock required the presence of at least two of the following: systolic blood pressure less than 90 mmHg; urine flow less than 20 mL/h; cool, clammy skin; and central nervous system dysfunction

A patient was considered to have diabetes if they were on glucose-lowering medication or diet at the time of admission or if the chart stated that diabetes was confirmed by appropriate tests during the admission.

Mortality in the general population

Age- and sex-specific population sizes for Halifax County were determined from census data. Age was aggregated in five-year age groups. Age-group and sex-specific all-cause and cause-specific deaths were derived from the Canadian Mortality Database (14). The mortality rate for the study population's age and sex peer group in the general population was calculated as:

$$\text{Population mortality rate} = (\sum nd_i \times w_i) / (\sum ps_i \times w_i)$$

where nd_i represents age group/sex-specific number of deaths (either all-cause or cause-specific), ps_i represents size of age group/sex-specific population and w_i represents fraction of age/sex group among the discharged AMI cohort.

Severity index

The patient characteristics (Table 1) were used to determine a case severity index that represented the probability of dying within five years following discharge after the index MI under the assumption that none of the interventions listed in Table 1 were

used. The method of calculating the severity index has been previously described (11).

Statistical procedures

Univariate analysis: Characteristics in patient profile, treatment pattern and medication use were compared across groups with χ^2 statistics for categorical variables. The median of skewed distributions for age, hospital stay and severity index were compared by median score test.

Multivariate analysis: Association between five-year survival and patient characteristics was assessed by logistical regression analysis. A stepwise selection procedure was used for the explanatory variables, testing all the patient characteristics and treatment variables listed in Table 1 for inclusion. The variable period was forced into the model to provide information with regard to residual period effect not explained by the explanatory variables. For the purpose of the logistical model, the variables that had 'unknown' as one of its states were recoded such that 'yes' versus 'no' or 'unknown' became the new variable states. The age of patients was grouped such that it divided the study population approximately into quartiles (quartile 1: 25 to 53 years; quartile 2: 54 to 61 years; quartile 3: 62 to 68 years; and quartile 4: 69 to 74 years). LV impairment was categorized into three levels: severe or shock, mild or moderate, or no impairment.

RESULTS

Evaluation of record linkage

During the time of MONICA data collection (1984 to 1993), the circumstances of the death of patients who had been registered by MONICA were reviewed. These cases were used to determine the sensitivity of the record linkage procedure. Of the 693 persons with known five-year mortality, the record linkage failed to find three cases (99.6% sensitivity). Similarly, an analysis of hospital readmissions identified 124 patients who were known to have survived the index event by five years or more. None of these cases were falsely identified by record linkage as fatal (100% specificity).

Study population

From January 1, 1984, to December 31, 1993, 4533 persons who had an index event that met the diagnostic criteria for inclusion in the study were identified. Of these, 3666 persons survived long enough to be discharged from the hospital. The in-hospital mortality had decreased from 22.9% in 1984 to 12.7% in 1993. The 3666 hospital survivors comprised the study population for the present study. Table 1 shows selected characteristics of the hospital survivors and their respective changes between the two study periods. Age and length of hospital stay had skewed distribution, which are illustrated by the respective quartile values. The types of MI were characterized by the proportion of Q-wave/ST elevation MI. The Q-wave and ST elevation classifications were combined to provide a consistent characterization throughout the study period, which spans the introduction of the two revascularization procedures thrombolysis and percutaneous coronary intervention (PCI). It was assumed that during the time when thrombolysis and PCI were not yet available, ST elevation MI would, in most instances, have presented as Q-wave MI.

Table 1 shows that there was no significant change in age distribution of MI patients between the two study periods. The prevalence of an Hx of MI, an Hx of hypertension, previous coronary artery bypass graft surgery (CABG), cigarette smoking

TABLE 1
Prevalence and average values of prognostic indicators among patients discharged after a myocardial infarction (MI) from 1984 to 1988 and from 1989 to 1993

Indicator	1984 to 1988 (n=1755)	1989 to 1993 (n=1911)	P
Patient characteristics			
Male sex, %	73.7	69	0.002
Median age, years	61	62	0.13
First quartile of distribution	53	53	
Third quartile of distribution	68	68	
MI with evolving Q-wave or STEMI, %	30	29.5	0.71
History of MI, %	29.1	30.3	0.46
History of hypertension, %	40.9	43.9	0.067
History of diabetes, %	16.7	19.3	0.04
Previous CABG, %	7.2	8.4	0.161
Previous PCI, %	0.51	5.6	0.001
Cigarette smoker, %	49.2	48	0.47
Mild/moderate left ventricular impairment after admission, %	32.9	50.3	0.001
Severe left ventricular impairment/shock after admission, %	12.9	7.1	0.001
Median severity index (range 0–1)	0.298	0.305	0.089
First quartile of distribution	0.19	0.20	
Third quartile of distribution	0.42	0.44	
Interventions			
CABG during index admission, %	3.8	8.1	0.001
PCI during index admission, %	4.4	13.5	0.001
Thrombolysis, %	7.1	29.9	0.001
ACE inhibitor at discharge, %	4.4	17.3	0.001
ASA at discharge, %	35.3	70.6	0.001
Beta-blocker at discharge, %	45.7	55	0.001
Median hospital stay, days	14	11	0.0001
First quartile of distribution	11	8	
Third quartile of distribution	18	15	

ACE Angiotensin-converting enzyme; ASA Acetylsalicylic acid; CABG Coronary artery bypass graft surgery; PCI Percutaneous coronary intervention; STEMI ST elevation myocardial infarction

and proportion of Q-wave/ST elevation MI were also essentially the same from 1984 to 1988 (period 1) and from 1989 to 1993 (period 2). A decline occurred in the length of hospital stay and the proportion of male patients. The prevalence of severely impaired LV function during admission decreased, but there was a larger increase in the prevalence of mild to moderate LV impairment, so that together more patients experienced some form of LV impairment while in hospital during period 2. The prevalence of an Hx of diabetes and PCI increased from period 1 to period 2. The increase in diabetes was possibly linked to an increase in body mass index in the general population of Halifax County, as noted in the risk factor surveys in 1984 to 1987 and 1995 (21). As expected, the prevalence of revascularization procedures during admission and the prescription of angiotensin-converting enzyme (ACE) inhibitors, acetylsalicylic acid (ASA) and beta-blockers at discharge increased, which was in line with treatment recommendations (22,23). During period 2, the association between mild to severe signs of heart failure during admission and prescription of ACE inhibitors at discharge was OR 2.07 (95% CI 1.60 to 2.68). Patients with shock during admission did receive ACE inhibitors at discharge at the same rate as patients without LV failure (OR 1.1; 95% CI 0.57 to 2.13).

Figure 1) Survival distribution functions for cases that occurred from 1984 to 1988 and from 1989 to 1993

Five-year survival

The average five-year survival was 74.8% during period 1 and 79.2% during period 2 ($P_{\chi^2}=0.001$). Figure 1 shows the survival distribution functions for the two study periods. It illustrates that the improved survival was not limited to a specific survival time but that the separation between the two curves increases progressively for all survival months. The difference between the two curves is statistically significant ($P=0.001$).

The logistical regression model estimating association between five-year survival and the prognostic variables of Table 1 provided a good fit for the data ($P=0.752$ for Hosmer-Lemeshow goodness-of-fit test). The results are shown in Figure 2. The variables whose prevalence changed significantly from period 1 to period 2 and that were, therefore, responsible for any change in survival, had the following ORs: men, OR=0.67 (95% CI 0.55 to 0.82); Hx of diabetes, OR=0.53 (95% CI 0.43 to 0.66); mild to moderate LV impairment after admission, OR=0.69 (95% CI 0.57 to 0.83); severe LV impairment/shock after admission, OR=0.40 (95% CI 0.31 to 0.53); CABG during index admission, OR=2.74 (95% CI 1.86 to 4.05); PCI during index admission, OR=2.63 (95% CI 1.67 to 4.14); thrombolysis, OR=1.98 (95% CI 1.50 to 2.62); ACE inhibitor at discharge, OR=0.56 (95% CI 0.44 to 0.72); ASA at discharge, OR=1.39 (95% CI 1.15 to 1.68); and beta-blocker at discharge, OR 1.60 (95% CI 1.34 to 1.92). The variable 'study period', which was forced into the model, was not significantly associated with five-year survival, implying that the remaining variables in the model are sufficient to account for the different survival pattern during the two study periods. To assess the effect of interpreting the clinical Hx values 'unknown' as 'no', the logistical regression model was repeated after replacing the values unknown with ones derived by multiple imputation procedure (24). This procedure resulted in only insignificant changes in the ORs.

Using the prevalence and strength of the effect to assess the relative importance for five-year survival of individual interventions shows that during period 1, the use of beta-blockers accounted for 47% of the survival benefit, followed by the use

Figure 2) The 95% CI for the OR of variables found to be significantly associated with five-year survival after discharge from hospital following an acute myocardial infarction (MI) between 1984 and 1993. ACE Angiotensin-converting enzyme; ASA Acetylsalicylic acid; CABG Coronary artery bypass graft surgery; LV Left ventricular; PCI Percutaneous coronary intervention

of ASA, which accounted for 22%. PCI, CABG and thrombolysis contributed less than 10% each because they were so rarely used. This changed significantly during period 2, when beta-blockers, ASA and thrombolysis contributed about equally to survival and together accounted for 75% of the population-attributable treatment effect. The exception during both periods was the use of ACE inhibitors; it affected survival negatively and its relative importance increased from period 1 to period 2.

Annual mortality rate

The annual mortality rate at the end of the first year of follow-up was 9.4% during period 1 and 6.5% during period 2. Thereafter, (ie, at the end of the second to fifth year of follow-up) the rate changed very little and averaged 4.66% during period 1 and 4.05% during period 2. For comparison, the annual mortality rate for the general population of Nova Scotia with the same age and sex composition as the MI patients was obtained from Statistics Canada (25). For 1996, that mortality rate was 1.57%.

Cause of death

The official cause of death for all 839 fatal cases was obtained, except for one fatality in the province of Ontario. The Registrar General of that province released the date of death, but not the cause of death. The distribution of causes of death did not differ significantly for the two study periods ($P_{\chi^2}=0.44$). At the end of the five-year follow-up period, MI or other CAD accounted for 52.6% of deaths; 16.7% were due to neoplasm; 11.2% were due to other vascular diseases; and 19.4% were due to other causes. There was a clear trend in the cause of death distribution with survival time, as shown in Figure 3. MI and other CADs became less dominant with increasing survival time, whereas neoplasm and other cardiovascular diseases contributed more to overall deaths. In the age- and sex-matched general population, the dominant cause of death was 'neoplasm' at 38.8%, followed by 'MI, and other CADs' at 27.7%, 'other' at 23% and 'other vascular disease' at 10.6%.

DISCUSSION

Our evaluation of the record linkage showed very high sensitivity and specificity. Applying these results to the cases without independent evidence of death from the MONICA AMI register, we conclude that we probably missed only one additional case. Therefore, our estimate of the trend in five-year survival can be considered quite accurate, although the shorter hospital stay during period 2 may have biased postdischarge mortality by including some deaths that would otherwise have occurred within the hospital. However, such bias was probably quite small because very few deaths occurred immediately after discharge.

Similar to Singh et al (4), we found that there was no difference in five-year survival between those with Q-wave/ST elevation MI and those without ST elevation or evolving Q-waves. Instead, survival during period 2 was improved if ventricular function was preserved by increased use of revascularization procedures or the decreased prevalence of severe LV impairment during admission.

The profile of patients discharged after an AMI changed from period 1 to period 2. The proportion of men among discharged MI patients was lower during period 2 because the proportion of men among patients admitted to hospital for MI decreased significantly, and because the patient fatality for hospitalized MI patients decreased for women but not for men. Also, a significant decline in the proportion of cases with severe LV impairment and an increase in those with mild to moderate LV impairment was noted between the two periods. With more and timely interventions in period 2, LV function was better preserved, resulting in fewer cases with severe LV impairment and, hence, more patients surviving to discharge. At the same time, the prevalence of diabetes and previous PCI increased significantly, with a marginally significant increase in the prevalence of Hx of hypertension. The increase in prevalence of previous PCI among MI patients was expected because PCI was used more frequently, either in elective or acute coronary syndrome cases. In our context, previous PCI and previous CABG can be viewed as markers for the presence of serious coronary disease, a well-known predictor of reduced survival. Presumably, this was also the rationale for the use of Hx of CABG for risk stratification by the Predicting Risk of Death in Cardiac Disease Tool (PREDICT) scoring scheme (26). All of the variables listed in Table 1 as patient characteristics have a negative effect on the probability of five-year survival; some variables increased, while others decreased in prevalence between period 1 and period 2. The median value of the severity index, representing the combined effect on survival of all of the patient characteristics, increased slightly between period 1 and period 2, but this increase was statistically not significant. It appears that the effect of counteracting trends in the characteristics cancelled each other out.

As expected, all interventions increased significantly and, as a group, they were positively associated with five-year survival, except for use of an ACE inhibitor, which had a negative association. The observed effect of ACE inhibitor use was in conflict with results from previous clinical trials (27,28), in which long-term survival benefits had been demonstrated. The apparent conflict is likely explained by the use of these agents at the time of the study because they were used frequently in patients with reduced LV function.

The improved treatment of AMI was demonstrated not only by increased long-term survival, but also by the cause of

Figure 3) Cause of death as a percentage of all deaths occurring per survival interval. AMI Acute myocardial infarction; CAD Coronary artery disease; Mo Month; Vasc Vascular; y Year

death of patients dying during the follow-up period. A Danish study (29) reported the eight-year survival of AMI patients discharged alive in 1963. This study found a five-year survival of 53.7%, and after eight years of follow-up, AMI and other heart diseases accounted for 74.4% of deaths. In our case, AMI and CAD caused only 52.1% of deaths after five years of follow-up, and that percentage would be even lower after eight years of follow-up, given the observed trend in Figure 3.

We found improved long-term survival for patients who were discharged alive after an AMI between 1984 and 1993 as a combination of unchanged case severity, but increased use of interventions. The same circumstances may not apply for more recent MIs. Since 1993, the use of some interventions has increased further, and the effectiveness of PCI has improved through the use of drug-eluting stents. However, case severity may have increased because between 1997 and 2001, the prevalence of diabetes among MI patients increased.

Our research demonstrated that while the long-term prognosis of MI survivors has improved, they are still at a much higher risk of dying than their age- and sex-matched peers in the general population. Not only was their annual mortality rate higher during each of the follow-up years, but they also died more frequently from AMI and coronary disease than those in the age- and sex-matched general population, suggesting the need for secondary prevention strategies.

Strength and limitations

The study was community based and includes all infarctions being hospitalized during the study period. The diagnosis of infarction was developed by a computer algorithm, reducing human bias. The research was observational and, therefore, could only identify associations but no cause and effect relationships. The study population was limited to the age group of 25 to 74 years. The cause of death was based on death certificate information and was, for the most part, not independently verified. At the time of our study, drug-eluting stents were not in use, which likely underestimates the beneficial outcome we found. Our study did not consider medical interventions that may have occurred after discharge. If our experience with readmitted MI patients is representative, then pharmacological intervention in the form of ACE inhibitors, ASA and

beta-blockers is maintained by more than two-thirds of the patients, even longer than two years after discharge.

CONCLUSION

While patient characteristics changed between 1984 and 1993, their combination did not alter the prognosis for five-year survival. Improved treatment during the acute event and increased use of discharge medication explain the improved five-year survival of the hospital survivors of MI. Cardiovascular death was the predominant mode of death over the ensuing five years following discharge after an acute MI.

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