Cardiovascular hospitalization as a surrogate endpoint for mortality in studies of atrial fibrillation: report from the Stockholm Cohort Study of Atrial Fibrillation

Leif Friberg1* and Mårten Rosenqvist2

1Department of Cardiology, Danderyd Hospital and Karolinska Institute at Danderyd Hospital, Stockholm, Sweden; and 2Department of Cardiology, South Hospital and Karolinska Institute at South Hospital, Stockholm, Sweden

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Aims

Cardiovascular (CV)-related hospitalization has been used as a surrogate endpoint for mortality in recent treatment studies on atrial fibrillation (AF), but our understanding of the relationship between CV-related hospitalization and death is incomplete. We aimed to investigate whether CV-related hospitalization is an independent risk factor and suitable as a surrogate endpoint for death in clinical studies of patients with AF.

Method and results

All 2912 patients with a diagnosis of AF in 2002 at one of Sweden’s largest hospitals were studied for 6.5 years using information about medication from the local medical records. In a sub-study of the last 2.5 years of the study period, we used detailed information about medication from the new National Prescription Register. Information about diagnoses, hospitalizations, and deaths was obtained from national registries. Patients who were re-admitted to hospital with a CV diagnosis within the first 3 months had higher mortality than those who were not (15.6 vs. 9.3 deaths per 100 patient-years at risk, \( P < 0.0001 \)). Those who spent >2% of their time-at-risk in hospital with a CV diagnosis had higher mortality than those who had spent less time in hospital (36.0 vs. 8.2 deaths per 100 patient years, \( P < 0.0001 \)). After adjustment for co-factors, mortality was still higher for patients who had been re-hospitalized for CV disease within 3 months than for those who had not [hazard ratio (HR) = 1.36; 95% confidence interval (CI) = 1.18–1.57]. When analyses were performed on patients who had survived for 3 years since inclusion, and with the use of detailed information about the exposure to medication, the association between CV-related hospitalization and death was highly significant (HR 2.69, CI 1.96–3.68). These results were virtually unchanged after propensity score matching, which was done in order to adjust further for residual unidentified confounding.

Conclusion

CV-related hospitalization is a marker for patients who are at increased risk of death, and may be used as a valid surrogate endpoint in studies of AF.

Keywords

Atrial fibrillation • Mortality • Surrogate endpoints • Cardiovascular hospitalization

Introduction

When a drug for a certain disease is introduced for the first time, the effects are often profound, as when William Withering began to use digitalis-containing foxglove to control heart rate in atrial fibrillation (AF) 200 years ago.1 Before that, AF was a malignant disease from which patients died within a few years, from tachycardia-induced heart failure.2 New and better drugs for treatment of AF have been introduced since then, but seldom if ever have the advantages of the new drug over the older one been as great as when compared with no treatment at all. Due to diminishing marginal gains, an ever-increasing number of patients must be included in studies of new drugs in order to make it possible to show superiority over a pre-existing standard treatment. One

* Corresponding author. Tel: +46701730519, Email: leif.friberg@ki.se

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way to circumvent this is by using composite or surrogate endpoints.

A good surrogate endpoint should occur more often than the true endpoint, should occur sooner than the true endpoint, and should be easy to detect. There should also be a strong relationship between the surrogate endpoint and the true endpoint. Cardiovascular (CV) hospitalizations have been proposed as a suitable surrogate for death.

Cardiovascular hospitalizations are more common than death; they occur sooner than death and they are easy to detect. The relationship between hospitalization and death also appears to be reasonably strong. In Sweden, approximately one-third of the elderly die in hospital and almost half of those who die do so within 14 days of hospital discharge. Cardiovascular-related hospitalization therefore appears to be a reasonable candidate marker of mortality. However, it remains to be evaluated whether the strength of the association is strong enough to make it suitable as a surrogate endpoint for mortality in AF studies.

The ATHENA trial regarding the efficacy of dronedarone in patients with AF used a composite of death from any cause and CV-related hospitalization as the primary outcome variable. The obvious reason was that it would generate more events and hence reduce the number of patients needed for the study. Nevertheless, ATHENA was a large trial involving almost 5000 patients. The number of patients needed in the study would have had to be several times higher if death alone had been the endpoint.

An evaluation of CV-related hospitalizations as a surrogate endpoint was performed on AF patients using data from the AFFIRM trial regarding rate or rhythm control in AF. An association with mortality was found, but there were study limitations, which called for new evidence of a confirmatory nature. In another study—not on AF patients specifically—of patients in the AVID (Anti-arrhythmics Versus Implantable Defibrillators) database, an association between new or worsened heart failure and impending death was found to exist.

Previous studies have shown that mortality among AF patients is about twice as high as in the general population, but most of this mortality can be attributed to underlying CV disease. Cardiovascular-related hospitalization may thus be seen as an indicator of the presence of underlying CV disease, whether known or as yet unknown. It may also indicate more advanced disease than in patients with the same diagnosis but without hospitalizations.

Aim

The aim of this article is to investigate whether CV-related hospitalization is an independent risk factor and is suitable as a surrogate endpoint for death in clinical studies on patients with AF.

Methods

The Stockholm Cohort Study on Atrial Fibrillation (SCAF) consists of all 2912 patients who received a diagnosis of AF or flutter while being treated as inpatients or outpatients at the South Hospital in Stockholm or at the Gustavberg Primary Care Centre (close to Stockholm) in 2002. The cohort has been followed since 2002 and has been described in detail in previous reports. At present, the data in the cohort represent >13,000 patient years at risk.

Patients were identified from the local registers at the hospital and at the primary care centre. Baseline information about the cohort was gathered from a scrutiny of the complete local computerized medical information, including physiological examination protocols and ECGs. To this end, a predefined protocol was used. Complementary information was obtained from the Swedish National Hospital Discharge Register, going back to 1987 nationally and to 1972 for Stockholm County. Information about important events (e.g., death, stroke, bleedings, myocardial infarction, and heart failure) was obtained through national registers.

Information about medication and rhythm status during follow-up was obtained through annual re-examinations of medical records up to 2005. From 1 July 2005 information about medication became available through the Swedish Medical Prescription Register. In this register, which lists all prescribed and dispensed medicine in the country, detailed information can be found about the strength, dosage, package size, date of prescription, and the date when it was handed over to the patient.

We found that the detail and completeness of this new information that became available in the middle of the follow-up period were so essential to the purpose of our study that we decided to perform separate analyses: one for the entire follow-up period of 6.5 years using information about the medication at baseline in the analyses, and another for the last 3.5 years where we had almost full knowledge of medications and could use drug exposure as time-dependent covariates in the analyses.

We calculated the exposure to medications from the information about the day on which a prescribed drug was handed over to the patient at a pharmacy, the quantity delivered, and the dosage prescribed. We could thus estimate on what days a patient was exposed to that drug. Regarding the exposure to warfarin, where doses vary over time, we estimated the exposure from dispensed, defined daily doses (DDDs) during time-at-risk. One DDD is defined as 7.5 mg of warfarin sodium, which may be somewhat higher than the doses used in an elderly population. Thus, we used an arbitrary cut-off at >80% of follow-up time with warfarin, above which we considered warfarin treatment to be continuous throughout follow-up.

When the Prescription Register started in July 2005, the original cohort of 2912 patients had been reduced to 2046 because of deaths that had occurred since 2002. At the time of writing, information about deaths and dispensed drugs was available up to 1 February 2009; whereas information about hospitalizations was available up to 1 January 2008. Thus, observation periods and time-at-risk varied depending on the endpoint of interest.

Definitions

For the definition of co-morbidities and previous diseases at baseline, we used the appropriate ICD-10 codes given in the Hospital Discharge Register. In addition, we used information from the local medical records regarding chronic conditions, which may occasionally evade reporting when more acute events are the cause of hospitalization. For example, we categorized patients as diabetics if they were using anti-diabetic medication or had more than two diagnostically elevated glucose tests, even if a diagnostic code for diabetes had not been used at discharge. Likewise, we categorized patients as hypertensives if there were at least two recorded blood pressure readings exceeding 160/95 mmHg, unless the readings had been obtained while the patient was in severe distress.
We used the same definition of CV-related hospitalization as in the ATHENA trial, which also included hospitalizations for certain surgical procedures, bleedings, and ill-defined diagnoses of symptoms such as chest pain. In the analyses, we counted hospital admissions as being CV if a CV diagnosis was used as the first or principal diagnosis.

Blanking and exclusions
We applied a blanking period of 30 days after the index event when registering re-hospitalizations. The reason for this was that entries in the National Hospital Discharge Register that occurred very early after the original index-generating hospital period were often due to transfer between clinics or hospitals, and not true re-hospitalizations. Furthermore, re-admissions that occurred early were often due to planned cardioversions and were thus related to the index event, and not true early re-hospitalizations.

We excluded 88 patients who died during the initial hospitalization period. The study was approved by the local Ethics Committee.

Statistical methods
For pairwise comparisons, t-tests and $\chi^2$ tests were used. For survival analyses, Kaplan–Meier analysis with the log-rank test and multivariable Cox regression was employed. The following time-dependent covariates were used: time to first CV-related hospitalization, fraction of time-at-risk spent in hospital with CV diagnosis, and exposure to certain medications expressed as a fraction of time-at-risk.

We dichotomized continuous variables for the sake of comprehensiveness for presentation in tables, but otherwise retained them as continuous as specified in each analysis.

Our strategy for the multivariable analyses was to move from no adjustment to more and more complex adjustments in order to see how the point estimates of the hazard ratios (HRs) changed. This was to ascertain the robustness of the analysis. Thus, from no adjustment we proceeded to adjustment for age and sex and then to adjustment for age and sex. Then we used the factors that were significantly associated with mortality after the simple adjustment for age and sex, and used that for the model—to which the remaining factors were added one at a time. This analysis was performed in two versions: one version with dichotomized data and another version with continuous data. Finally, we performed the analysis again according to a stepwise forward procedure in which the computer chose which variables were significantly associated with the outcome variable, and with a procedure where we chose factors for the model that are well known to be strongly associated with mortality. The factors that were used for each analysis have been listed under the tables. Overlapping—or obviously interdependent—covariates were not used simultaneously in any of the analyses.

In order to further take into account the differences in patient characteristics between patients who had had an early CV-related hospitalization and those who had not, we used propensity scores. The use of propensity scores is widely accepted as a tool to increase comparability and to reduce the potential influence by confounding in non-randomized studies. For the identification of factors associated with early hospitalization, we used logistic regression with all of the factors listed in Table 1 in the model. From the logistic regression, we obtained scores for the likelihood of CV-related hospitalization for each individual based on the available information that was entered into the analysis. Those patients with and without early CV-related hospitalization were matched on the basis of identical propensity scores. Then multivariable Cox analysis was applied to the groups that we had tried to make similar regarding baseline characteristics.

All tests were two-sided. Confidence intervals (CI) were 95%. P-values $<0.05$ were considered significant. All analyses were performed using SPSS 17.0 and PASW 18.0.

Results
Unadjusted mortality
During $\sim6.5$ years of follow-up, 48% of the patients died (1368/2824). Of the patients who died, those who had been re-hospitalized with a CV-related diagnosis had slightly shorter survival ($2.0 \pm 1.8$ years counted from the date of re-hospitalization, $n = 770$) than those who were not re-hospitalized ($2.2 \pm 1.9$ years counted from the index date, $n = 598$). There were considerable differences at baseline between patients who died and those who survived (Table 1). The patients who died were older than the survivors (mean 80 vs. 68 years, $P < 0.0001$) and were more ill and frail in almost every respect.

Mortality in the cohort was almost twice as high as in the general population after adjustment for age and sex (standardized mortality ratio 1.8, CI 1.7–2.0). Death from any cause occurred at a rate of 9.9 per 100 patient years at risk. The combined endpoint CV-related hospitalization (as first diagnosis) occurred at a rate of 19.1 per 100 patient years at risk.

We performed a separate study of the period starting 1 July 2005, for which we had information about medication from the Prescription Register. At the start of this period, patients from the original cohort were still alive. During follow-up, 419 other patients died (20%), representing 9.2 deaths per 100 patient years at risk. Characteristics of this subset of patients, with new baseline data regarding conditions in 2005, are also given in Table 1.

Mortality was higher in patients who had been re-hospitalized in the first 3 months than among those who had not (15.6 vs. 9.3 deaths per 100 patient years, $P < 0.0001$; Table 2). Patients who spent $>2\%$ of their time-at-risk in hospital with a CV-related diagnosis had a particularly poor prognosis as compared with patients who spent less time in hospital (36.0 vs. 8.2 deaths per 100 patient years, $P < 0.0001$).

Reasons for re-admission
We studied the specific causes of the first re-hospitalization in patients who had been re-admitted with a CV diagnosis and found that AF was the principal diagnosis in 44%, heart failure in 17%, a thrombo-embolic event in 15%, and ischaemic heart disease or chest pain in 14%. Other CV diagnoses accounted for the remaining 10%. The prognosis varied widely, with a poor outcome for patients with heart failure and thrombo-embolic events and a relatively good prognosis for patients with AF as the main diagnosis (Figure 1).

Mortality after adjustment for co-factors
After adjustment for 31 co-factors, mortality remained higher for patients who had been re-hospitalized for CV disease within 3 months than for patients who had not. We used different models for the Cox analysis in order to ascertain the robustness of data. We tried using variables in both dichotomized and continuous modes, we entered covariates in automated stepwise
forward mode, we entered them as found relevant from the finding of other studies, and we entered variables that were significantly associated with mortality in the univariate analyses. Whichever way we constructed the multivariate models, the point estimates for the HR remained constant in the narrow range of 1.33–1.40, all with P-values <0.0001 (Table 2). These results were virtually unchanged after propensity score matching, which was done in order to adjust for residual unidentified confounding.

The association between CV-related hospitalization and mortality appeared to be stronger when related to how much of the time-at-risk in
hospital with a CV diagnosis were more likely to die than those who spent less time in hospital (HR 2.35–2.48, P < 0.0001). There was also an association between mortality and time spent in hospital before entering the study. Patients who had been in hospital for >10 days during the preceding 3 years had a higher risk of dying during follow-up (HR 1.27–1.33, P < 0.0001).

We performed all the analyses again for the observation period 2002–08 without using the 30-day blanking period at the beginning, and obtained similar results as when blanking was used (not shown).

When we postponed the start of the observation period to July 2005 in order to be able to use information about medication, almost one-third of the cohort had died. At the new baseline date, the mean age in the cohort was almost the same as it had been in 2002 despite the fact that everyone had become 3 years older. The apparent paradox was due to balancing effects of uniform aging of the cohort, and high death rates among the oldest (Table 1). The prevalence of concomitant disease and the fractions of patients using warfarin, anti-arrhythmics, and other medication showed great resemblance between the cohorts in 2002 and the cohorts in 2005. One important difference, however, was the duration of AF. At baseline, approximately one-third of the patients had newly presented AF, whereas in the cohort of 2005 all had a history of AF for at least 3 years.

Patients who were re-hospitalized within 3 months of the new index date in 2005 had higher mortality than those who were not (18.0 vs. 8.6 deaths per 100 patient years at risk, P < 0.0001; Table 3). We also found that the association between re-hospitalization within the first 3 months and death (HR 2.43, CI 1.78–3.32, P < 0.0001; Table 3) appeared to be stronger when analysed with more information about medication than when analysed using only information about baseline medication in 2002 (HR 1.40, CI 1.21–1.61, P < 0.0001).

The association between death and how much of the time-at-risk had been spent in hospital with a CV diagnosis was found during the first and longer observation period, which was found during the first and longer observation period, was also found in this later observation period (HR 3.16, CI 2.29–4.36, P < 0.0001; Table 3).

### Discussion

We found a strong association between CV-related re-hospitalization and mortality in AF patients. Without adjustment for co-factors, this is exactly what was expected, because it is illness, and hence increased risk of dying, that make people go to hospital. What was remarkable was that the highly significant association between CV-related hospitalization and death
remained even after adjustment for an unusually full and detailed list of co-factors acquired through national Swedish healthcare registries.

Our interpretation is that there must be important residual confounding that cannot be accounted for by the information available in medical records and registers. The most important reason for this is probably that the information about the degree of disease may vary in medical records, and may be poor or absent in national registries. The code for hypertension, I10, is used for all forms of hypertension, borderline as well as malignant. The same applies to the code for heart failure or almost any diagnosis. When decisions about hospital admission are made in the emergency room the doctor uses his/her experience or intuition to differentiate patients according to the severity of disease. Likewise, the patient makes decisions about whether or not to go to hospital based on his or her own appreciation of the severity of the problem. Thus, a constant selection process is at work to preferentially hospitalize the sick and to let the healthier remain at home, even in patients with the same diagnosis or medication.

Furthermore, there are factors of importance for survival that are seldom documented in records or registries. Examples of such factors are smoking, drinking, fitness, loneliness, poverty, obesity, and other lifestyle factors known to affect survival. Thus, for practical purposes, CV-related hospitalization appears to be an independent risk factor for mortality.

The relationship between CV-related hospitalization and mortality was stronger when measured as relative time in hospital (days in hospital divided by days at risk of dying) rather than as time to first re-hospitalization. The relative time in hospital is probably a more sensitive measure of the severity of disease than the time to first re-hospitalization, which may be for a minor or benign cause. However, fractional time-at-risk in hospital does not work well as an endpoint in a study. For this purpose, the time to first re-admission with a CV diagnosis is more suitable. It may also be amalgamated with all-cause, or cause-specific, mortality.

### Table 3 Multivariate analyses regarding all-cause mortality within 2.5 years in 2046 patients

<table>
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<tr>
<th>Level</th>
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<th>Died</th>
<th>Deaths per 100 patient years</th>
<th>Any cause of death between 1 July 2005 and 1 January 2008</th>
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<td>Univariable</td>
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<td>HR  95% CI</td>
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<td>Within 3 months</td>
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<td>Yes  139 49 (35%)</td>
<td>18.0</td>
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<td>No  1907 370 (19%)</td>
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<td>Within 6 months</td>
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<td>Yes  258 88 (34%)</td>
<td>16.9</td>
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<td>No  1788 331 (19%)</td>
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<td>Within 12 months</td>
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<td>Yes  460 128 (28%)</td>
<td>13.2</td>
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<td>No  1586 291 (18%)</td>
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<td>Percentage of follow-up in</td>
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<td>≥5%  78 61 (78%)</td>
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<td>&lt;5%  1968 358 (18%)</td>
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Total time-at-risk was 4563 years.

Factors used in the multivariate Cox model were: cardiovascular-related hospitalization within 3 months; age; sex; fraction of follow-up time with a class 1 or 3 anti-arrhythmic agent, a beta-blocker, digoxin, angiotensin-converting enzyme inhibitor/A2-blocker; statin, warfarin, or aspirin; permanent type of atrial fibrillation; heart failure; valvular defect; previous ischaemic stroke; peripheral arterial disease; chronic pulmonary disease; renal failure; diabetes mellitus; cancer within the last 3 years; or a previous hospitalization period within 3 years prior to the diagnosis of alcohol or drug abuse.

**Figure 1** Survival in relation to the principal diagnosis at the first cardiovascular-related re-hospitalization. AF, atrial fibrillation (n = 469); IHD/Chest pain, ischaemic heart disease or admission due to unspecified chest pain (n = 139); Thrombo-embolic, ischaemic stroke or TIA, arterial or pulmonary embolism (n = 116); CHF, congestive heart failure (n = 146); Other, all other cardiovascular diagnoses (n = 108). Differences were statistically significant between all groups except between ‘Thrombo-embolic’ and ‘CHF’ and between ‘Thrombo-embolic’ and ‘Other’.
mortality as a composite endpoint. In this study, this combined endpoint occurred approximately twice as often as death alone, which is of great importance for reducing the number of patients necessary in a study.

The specific cause of re-admission was shown to be important for the prognosis. If it was AF, the prognosis was much more favourable than with any other diagnosis (Figure 1). The most likely reason for this was not only the absence of other severe illnesses, but also the fact that elective re-hospitalizations for DC-cardioversions and initiation or changes of drug treatment under telemetric surveillance occur frequently in patients with AF as the principal diagnosis. Thus, it is to be expected that exclusion of the AF diagnosis from the endpoint CV-related hospitalization would make its association with mortality even stronger, and thus better as a surrogate endpoint. We tried to minimize the effects of such elective re-hospitalizations by applying a 30-day blanking period at the beginning of the observation period, but found that the results were essentially the same with either method.

This finding is in agreement with the results of a post hoc analysis that was performed on the data of the AFFIRM trial. In the absence of recorded data on the various CV reasons for re-hospitalization in the AFFIRM study, data were analysed both in an all-inclusive fashion and with exclusion of events ‘that occurred in the same follow-up period as a cardioversion or drug change’. Exactly how long this blanking period lasted was not specified in the report. Nevertheless, the methodology appears to have been essentially the same as the one used in our study. In both studies, the association of CV-related re-hospitalizations with mortality remains strong and highly significant irrespective of whether data are diluted by inclusion of re-hospitalizations for benign causes.

The endpoint CV-related hospitalization and hospitalization for any cause are good as endpoint in their own right, reflecting both the quality of life of the patients and the cost of treatment for the care-givers. When used as surrogate for death in combined endpoints, however, planned re-hospitalizations for cardioversions, drug initiation, or ablation ought not to be counted as CV related.

In the AFFIRM post hoc analysis, CV-related re-hospitalization was just as ominous a finding, irrespective of treatment strategy. This is an important finding, since a valid surrogate endpoint should not differ by treatment assignment in its association with the true endpoint of interest, i.e. death.

Our study represents approximately the same number of patient years at risk as the AFFIRM study, but with adjustments for more than twice the number of co-factors. Furthermore, we tried several different methods of adjusting for co-factors, all of which yielded similar results. This indicates that the results have a high degree of robustness.

In the AVID trial, which compared survival with anti-arrhythmic medication and with implantable defibrillators, an analysis of the validity of re-hospitalization as a surrogate endpoint for death was also performed. This trial did not deal exclusively with AF patients, and it consisted of patients with very high risk of dying from arrhythmia. However, the study did record the principal diagnosis for re-hospitalization, and it was found that the strongest predictor of death was a new or worsened heart failure. Our finding that there is an approximately doubled mortality rate in patients re-hospitalized with a first diagnosis of heart failure rather than of AF confirms the observations of the AVID trial in another set of patients with AF and generally with a lower risk of sudden death.

Methodological considerations

One strength of the present study was that we had access to national health records dating back several decades for all patients. Furthermore, for the latter part of the observation period we even had detailed information about the medication used, not only at the time of inclusion but also continuously throughout the observation period. This allowed far better control of confounding co-factors than is usually the case in retrospective studies of registries and medical records. Another strength of the study was that the results were consistent across several different methods of analysis.

There are, however, important limitations in studies of registries and records. Shades and degrees of the severity of a disease are reduced to a binary yes or no. A patient with the heart failure code I50 may be in NYHA class I with minimal symptoms, or in NYHA class IV with pulmonary oedema. Behind the code I10 for hypertension might be a patient with a systolic blood pressure of 145 mmHg or someone with 270 mmHg. We cannot tell the difference from the registries, but it is obvious that differences such as these are important for the outcome.

We were generally unable to make adjustments for important lifestyle factors such as smoking, drinking, fitness, obesity, and socioeconomic status, because information about such circumstances is mostly absent in national registries. The information that can be found in local medical records is sporadic and may even be deliberately omitted by doctors out of respect for the patient’s integrity. (In Sweden, by law, patients have a right to read their own medical records.) For the variable ‘alcohol abuse’, we counted patients who had attended hospital at some time with a diagnosis of alcohol abuse, alcohol intoxication, alcohol dementia, or another clearly alcohol-related diagnosis, in full knowledge of the fact that this only identified a minority of particularly advanced alcoholics.

Some re-hospitalizations were without doubt by appointment, for reasons discussed above. We regret that we did not take note of such circumstances when we read the hospital records. Unfortunately, this information cannot be extracted from the national registries. Had we been able to exclude planned hospitalizations from the analyses, our belief is that the association between unplanned CV-related hospitalizations and mortality would probably have been even stronger. We tried to make up for this by using a 30-day blanking period at the beginning of the study, but we understand that this is not a perfect solution to the problem.

The lack of precision and detail in the information that is inherent in studies of records and registries may attenuate and obscure real relationships. We consider it improbable that the above-mentioned limitations of our study would have resulted in an overestimation of the strength of the association between re-admissions and death.

The patient group studied consisted mainly of an urban, hospital-based, white population with a high mean age and considerable
co-morbidity. It is not certain whether the results are applicable to any other set of patients.

Conclusion
Cardiovascular-related hospitalization is a marker for patients at increased risk of dying and may be used as a surrogate endpoint in studies of AF.

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