Prognostic impact of different regional referral practices for interventional investigation and coronary treatment after exercise testing: a population-based 5-year follow-up study

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Objective. To examine the association among different centres’ referral practices for coronary angiography (CAG) after exercise testing, with 1- and 5-year outcomes.

Design. Observational population-based cohort study.

Setting. All 10 hospitals and six private practising consultants in Aarhus and Ringkøbing counties (900 000 inhabitants), Denmark.

Subjects. All patients who in 1996 had an abnormal bicycle exercise test (n = 736).

Measurements. Referral for CAG, coronary intervention, cardiovascular and all-cause mortality, and myocardial infarction (MI).

Results. As an immediate consequence of the exercise test, 60.7% of subjects were referred for CAG. Based on the centres’ fraction of patients referred for CAG, three categories of centres were defined: low (<33%), intermediate (33–66%) and high (>66%). A low compared with a high referral fraction was associated with a similar 5-year mortality and MI ratio [all-cause/cardiovascular mortality rate ratio (RR) = 1.33, 95% confidence interval (CI): 0.45–3.92/RR = 0.62, 95% CI: 0.25–1.57; and MI RR = 0.92, 95% CI: 0.45–1.86]. The same was found for an intermediate compared with a high fraction (all-cause/cardiovascular mortality RR = 0.92, 95% CI: 0.49–1.72/RR = 0.74, 95% CI: 0.42–1.33; and MI RR = 1.07, 95% CI: 0.68–1.70). Estimates were about the same after 1 year of follow-up with no major differences among centres in mortality or MI.

Conclusions. Centres’ different referral practices for interventional investigation and treatment were not associated significantly with short-term or long-term mortality or MI among patients with an abnormal exercise test.

Keywords: coronary angiography, doctor’s practice patterns, exercise test, myocardial revascularization, treatment outcome.

Introduction

Regional variations in everyday clinical practice that cannot be explained by severity of illness or patient preference are well known [1]. The health consequences of these variations are scantily explained. Coronary angiography (CAG) is the main diagnostic evaluation used to determine referral for coronary revascularization. Doctors’ referral to this procedure also varies considerably among regions [2–4], but little is known about the impact of different regional referral practices for CAG on cardiovascular morbidity and mortality.
In a recent cross-sectional study of baseline data of our population, we reported similar bicycle exercise testing rates in two Danish counties, but despite the conclusion of an abnormal test, referrals to CAG were quite different. In the county that had no local angiography centre, the CAG activity was approximately half that of the county hosting the angiography centre serving both counties. The fraction of patients referred for CAG decreased with increasing distance to the CAG centre [5, 6]. Increased cardiovascular morbidity and mortality with decreasing referral for CAG might be expected.

The aim of this long-term follow-up study, using medical records and population-based registry data, was to examine the prognosis [cardiovascular and all-cause mortality, and myocardial infarction (MI)] for patients with an abnormal exercise test examined in centres with different referral practices for CAG.

Methods

We conducted this follow-up study in two Danish counties, from 1996 to 2001. The study population included all residents of Aarhus and Ringkøbing counties, with 625,000 and 275,000 inhabitants, respectively (a total of 18% of the Danish population). Within the two counties, there is one university hospital (two departments of cardiology); a total of nine district hospitals (four and five, respectively); and six private cardiology consultants (three and three, respectively).

Denmark is divided into 15 counties and regions responsible for health care. The Danish health care system is public, administered by the National Health Service in each county, and funded by taxes. This system ensures free medical care and access for all citizens to general practitioners, private consultants and hospitals.

Since 1968, all Danish citizens have been given a unique 10-digit civil personal registration number (the first six digits are date of birth). This number is used in all Danish registries and permits record linkage.

All hospitals and private cardiology consultants of the two counties carried out exercise stress testing and decided independently on referral for CAG. A single team of cardiologists and heart surgeons at the Aarhus University Hospital determined the therapeutic measures to be taken following CAG.

Data on use of exercise testing and referrals

All patients (2763) who submitted to a bicycle exercise test in the two counties during 1996 were identified by a procedure code. Patients examined at hospital were identified in the County Hospital Registries. Patients examined by private consultants were identified in the National Health Service Registries – a county registry of accounts according to examinations performed by the private consultants. All the patients were suspected of ischaemic heart disease and were free of symptoms of angina at the beginning of the test (stable angina).

Medical records were systematically reviewed to obtain information about the result of the exercise test, the doctors’ conclusion on the basis of the exercise test results and the referral outcome. All centres performing bicycle exercise testing registered exercise-induced electrocardiographic ischaemia, symptoms of angina, and drop of blood pressure below the resting value, as evaluation points.

Doctors used three conclusion categories: normal, abnormal or inconclusive. We included only patients for whom the conclusion of the exercise test was abnormal (n = 736). All others (n = 2027) were excluded.

We used two categories to characterise the consequence of an abnormal exercise test: (i) the doctor referred the patient for CAG; or (ii) the doctor did not refer the patient for CAG. For all referred patients, the waiting time for CAG and the waiting list was similar.

Three groups defined

Based on the fraction of each centres’ patients with abnormal exercise test referred for CAG as an immediate consequence of the exercise test, centres were categorized into three referral groups: a low group (<33% referred for CAG; eight centres), an intermediate group (33–66% referred for CAG; six centres), and a high group (>66% referred for CAG; three centres).

Data on time to CAG

We linked patients with an abnormal exercise test to the County Hospital Discharge Registries to obtain
the date of an eventual CAG during the first 3 years after the testing. Both CAG performed as a consequence of the exercise test and CAG performed due to later referral were registered.

Data on outcome and co-morbidity

The Danish Central Personal Registry is updated daily and includes citizens’ name, address, vital status (death or migration), date of changes in status and familial relations (i.e. marital status, children and parents). From this registry, we obtained data on date of death and/or migration. During the follow-up period, we identified one person with an abnormal test who migrated (0.14%).

The Danish National Registry of Patients was founded in 1977 and includes information about all patients admitted to nonpsychiatric hospitals in Denmark [7]. We linked each patient who had an abnormal exercise test to this registry and obtained all discharge diagnoses and surgical procedures registered from 1 January 1977 to 31 December 2001.

The Danish Mortality Files have been in operation since 1943 and include data on all deaths of Danish residents in Denmark [8]. From this registry, we collected data on the cause of death. For patients who died prior to 1 January 2000, the registry data were computerized. For patients who died during 2000–01, the cause of death was not yet computerized and therefore was manually extracted from the death certificates.

Discharge diagnoses and causes of death were classified according to the Danish version of the International Classification of Diseases (ICD), 8th and 10th Revision – classified by ICD-8 through 1993, and ICD-10 thereafter. (The ICD-9 was never introduced in Denmark.) The surgical procedures were classified according to the Danish version of the International Classification of Surgical Procedures through 1995, and thereafter according to the Danish version of the Nordic Classification of Surgical Procedures. Discharge diagnoses and surgical procedures are coded at discharge by hospital doctors.

Co-morbidity index

From discharge diagnoses, the burden of co-morbid disease to baseline was estimated using the Charlson co-morbidity index [9–11] (Appendix 1). A history of previous MI to baseline was excluded from the index calculation and used separately in the analyses. The weights of the co-morbidity index of the study population were calculated and were in agreement with the original weights calculated by Charlson.

Statistical analysis

The times from exercise test to death (by all causes or restricted to cardiovascular causes), MI, referral to CAG examination and bypass operation (CABG), or percutaneous coronary intervention (PCI) were calculated. All patients were followed from the date of bicycle exercise test until death, migration, or 31 December 2001, whichever came first. The crude curves describing the development of the risk of death, MI, CAG examination, and coronary intervention over time were estimated by the Kaplan–Meier estimates. The Cox proportional hazard model was used to study the association between the fraction of patients referred for CAG (low, intermediate or high) at the time of exercise testing and time to events, adjusted for potential confounders (age, gender, previous MI and co-morbidity) [12].

Risk estimates are presented as rate ratios (RR). For patients who had a bypass operation or a PCI during follow-up, the risk estimate was adjusted by

Appendix 1 Scoring of the comorbidity index from discharge diagnoses, Charlson index

<table>
<thead>
<tr>
<th>Weights</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| 1       | Congestive heart failure  
          Peripheral vascular disease  
          Dementia  
          Cerebrovascular disease  
          Chronic pulmonary disease  
          Connective tissue disease  
          Ulcer disease  
          Mild liver disease  
          Diabetes                                                          |
| 2       | Hemiplegia  
          Moderate or severe renal illness  
          Diabetes with end organ damage  
          Any tumour                                                          |
| 3       | Leukaemia  
          Lymphoma                                                          |
| 4       | Moderate to severe liver disease                                   |
| 5       | Metastatic solid tumour  
          AIDS                                                              |
including a time-dependent variable according to the date of intervention [13, 14]. This corresponds to the common practice of censoring the observations at the intervention time for effects of estimation of the RR before intervention, and use of the remaining observation (after intervention) period for estimating the RR postintervention.

The model was validated by classic goodness tests and tests for the proportionality assumption [13, 14]. Statistical analysis was performed with the SAS software (version 8.02, SAS Institute, Cary, NC, USA).

**Results**

As an immediate consequence of the exercise testing, a total of 60.7% of the patients were referred for CAG. The median waiting time was 133 days, and 12.1% died during waiting time. We found no significant differences in the proportion of deaths during the waiting time to CAG between the three groups of patients (Fischer’s exact test). Table 1 summarizes the demographic characteristics, baseline and follow-up data of all patients from the two counties with an abnormal bicycle exercise test in 1996, grouped according to the centres’ fraction (low, intermediate or high) of referral for CAG at the time of exercise testing. Overall, 24.7% of the examined patients were women and 38.7% had a history of MI prior to the exercise test. According to age, gender, history of MI at baseline, and ischaemic parameters during the exercise testing, the three groups of patients were almost identical.

**CAG examination**

Figure 1 shows the cumulative incidence of the patients in each group, examined with CAG during

| Table 1 Baseline and follow-up data according to fraction of referral for coronary angiography (CAG) when there is an abnormal bicycle exercise test result |
|---------------------------------|-----------------|------------------|-----------------|
| **Fraction of patients referred for CAG** | **Low (<33%)** | **Intermediate (33–66%)** | **High (>66%)** |
| No. of patients | 97 | 422 | 217 |
| Gender (m/f) | 75/22 (71.3% m) | 316/106 (74.9% m) | 163/54 (75.1% m) |
| Age at exercise testing year |  |  | |
| Mean | 61.7 | 59.4 | 61.2 |
| Quantiles |  |  | |
| 25 | 56.2 | 52.8 | 54.3 |
| 50 (median) | 61.8 | 59.8 | 62.2 |
| 75 | 67.4 | 65.8 | 69.2 |
| History of MI at exercise testing | 37 (38.1%) | 165 (39.1%) | 83 (38.3%) |
| During exercise testing |  |  | |
| Angina | 42 (43.3%) | 243 (57.6%) | 98 (45.2%) |
| ECG ischaemia | 83 (85.6%) | 380 (90.0%) | 187 (86.2%) |
| BP drop | 11 (11.3%) | 32 (7.6%) | 17 (7.8%) |
| Referred for CAG at exercise testing | 27 (27.8%) | 248 (58.8%) | 172 (79.3%) |
| Person-years of follow-up to death | 500 | 2151 | 1108 |
| Person-years of follow-up to MI | 461 | 1951 | 1006 |
| CABG/PCI during follow-up | 32/16 | 145/147 | 64/78 |
| Death during follow-up |  |  | |
| Cardiovascular |  |  | |
| 1 year | 2 (2.1%) | 11 (2.6%) | 8 (3.7%) |
| Entire | 6 (6.2%) | 31 (7.3%) | 20 (9.2%) |
| Of all causes |  |  | |
| 1 year | 4 (4.1%) | 15 (3.5%) | 13 (6.0%) |
| Entire | 11 (11.3%) | 58 (13.7%) | 35 (16.1%) |
| MI during follow-up |  |  | |
| 1 year | 9 (9.3%) | 33 (7.8%) | 19 (8.8%) |
| Entire | 11 (11.4%) | 58 (13.7%) | 28 (12.9%) |

MI, myocardial infarction; CABG, coronary angiography bypass; PCI, percutaneous coronary intervention.

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the 3-year period after exercise testing. The RR of the intermediate group compared with the high group was 0.66 (95% CI: 0.54–0.80). The RR of the low group compared with the high group was 0.32 (95% CI: 0.23–0.45).

CABG/PCI

Figure 2 (a,b) shows the cumulative incidence of patients in each group who had CABG or PCI during the entire follow-up period. A total of 33.0%/34.4%/29.5% of the patients examined in centres with low/intermediate/high fraction referred had a bypass operation. There was no difference in CABG activity among the three groups: low compared with high (RR = 1.09, 95% CI: 0.70–1.68), and intermediate compared with high (RR = 1.15, 95% CI: 0.85–1.55).

The cumulative incidence of PCI according to group (low, intermediate or high) during follow-up was 16.5, 34.8 and 35.9%, respectively. The RR of the low group compared with the high group was 0.37 (95% CI: 0.21–0.65). There was no difference between the intermediate and the high groups (RR = 0.92, 95% CI: 0.69–1.22).

Mortality and MI

Figures 3, 4 and 5 show the cumulative incidence of cardiovascular and all-cause mortality and MI, according to the group (low, intermediate or high referral fraction). As seen in Table 1, cardiovascular deaths accounted for 66% of all deaths after 1 year and 55% in the entire follow-up. The MI rate was highest in the first year after exercise testing. After 1 year and during the entire follow-up period, there were no substantial differences in cardiovascular mortality, all-cause mortality or RR of MI among the three groups (Table 2). Analyses with the private consultants excluded did not change the estimates.
Discussion

We found, in this population-based long-term study of 736 patients with known or suspected stable ischaemic heart disease and with an abnormal exercise test, that highly different post-test referral practices to CAG do not appear to be associated significantly with the outcome of cardiovascular disease.

We compared three groups of patients who in all cases could be considered as comparable. They were of the same age, had a similar history of MI and bypass operation during follow-up. The difference among the three groups in the ischaemic parameters during exercise testing was included as a potential confounder in the analyses. The only obvious difference was exposure to different referral practices for coronary evaluation after an abnormal exercise test. The different referral practices seen at baseline continued during the following 3 years.

Outcome of an illness depends on age, gender, underlying diseases, accuracy and utility of diagnostic tests, coronary interventions, clinical performance and patient compliance [15]. Several aspects are covered in our study. The most interesting finding of our study was that a conservative referral practice after abnormal exercise testing does not appear to influence either short- or long-term outcome. Their triage according to immediate consequence of the exercise test was associated with a similar outcome obtained by doctors with a more invasive approach. Our data indicate that the doctors, with the aid of exercise testing, can distinguish between lesser and more severe coronary disease in patients. Our finding of a similar prognosis irrespective of local practice for referral to CAG is in line with the very limited number of studies concerning the consequences of (regional) different referral practice to CAG after MI [16–23]. This is in contrast to a study where the rates of

<table>
<thead>
<tr>
<th>Fraction of patients referred for coronary angiography</th>
<th>Cardiovascular mortality ratios</th>
<th>All-cause mortality ratios</th>
<th>MI ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted* (95% CI)</td>
<td>Crude</td>
</tr>
<tr>
<td>1 year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;33%)</td>
<td>0.55</td>
<td>0.62 (0.25–1.57)</td>
<td>0.68</td>
</tr>
<tr>
<td>Intermediate (33–66%)</td>
<td>0.71</td>
<td>0.76 (0.43–1.36)</td>
<td>0.59</td>
</tr>
<tr>
<td>High (&gt;66%)</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Entire follow-up</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intermediate (33–66%)</td>
<td>0.80</td>
<td>0.74 (0.42–1.33)</td>
<td>0.85</td>
</tr>
<tr>
<td>High (&gt;66%)</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
</tbody>
</table>

*Adjusted for gender, age, co-morbidity and previous MI. Further adjustment for coronary intervention (bypass operation or percutaneous coronary intervention) during the follow-up period as a time to time dependent variable did not change the estimates.

angiography were inversely related to the risk of death from heart disease [24]. In contrast to other studies our study population was based on all patients with an abnormal exercise test, both with and without previous MI, although representing a daily clinical problem and question, referral for CAG or not after an abnormal exercise testing.

Our finding of a selection of patients with the most severe coronary disease for CAG in hospitals/private consultants with low fraction of referral is supported by our finding in recent studies of the present population. In line with other studies [18], patients (men) from a region with the low CAG rate generally had more severe coronary disease than patients referred from a region with high CAG rate [5]. If this is the case, the strategy of referral concerns patients with less severe coronary disease – a group where an invasive strategy compared with medical treatment does not improve survival or risk of MI [25, 26].

Strengths and limitations

Our study has both strengths and limitations. The major strength of the study lies in its comprehensive nature and degree of completeness. All examined patients from a geographically defined population were identified. There was a complete follow-up in registries on the basis of central personal registration numbers; eventual co-morbidity was also considered.

By the use of routine data, bias was avoided in the specialist’s interpretation and choices about therapeutic consequence of the exercise tests. All bicycle exercise tests were interpreted by cardiology specialists, and there were no economic restrictions upon referral of patients from any of the hospitals or private consultants to the CAG centre; nor were there any principal or political difference between the two counties in their management of health care problems.

We had access to data about age, gender, co-morbidity and previous MI. However, residual confounding, due to different degrees of necrosis after MI, or different severity of heart disease of patients examined in different centres could not be taken into account. As patients were examined at the regional hospital or by the local private consultant, there is no reason to believe in a fundamental difference in the severity of heart disease in patients examined by different hospitals/private practising specialists.

The use of disease-specific mortality (in this case, cardiovascular) or all-cause mortality as the fatal end-point can be discussed, due to validity problems with a disease-specific end-point that rests on the assumption that the cause of death can be accurately determined [27]. Categorizing the major cause of death is based on autopsy findings in very few cases and on clinical judgement in most cases. The largest categorizing problems are traditionally within the cardiovascular diseases [28–30]. There is a risk of overestimation due to misclassification of patients with sudden unexpected death who often are categorized as cardiovascular death. Contrarily, the use of cardiovascular death as the end-point can exclude patients whose cardiovascular disease contributes seriously to death, but is overruled by another fatal condition.

Another well-known limitation of register data is that diagnosis at discharge is not uniformly accurate. A validation of the MI diagnosis of the Danish National Registry of Patients showed about a 90% agreement with the medical records [31, 32], i.e. there is a possible underestimation of the MI ratio. There is no reason to believe in different validity of the registration among regions or centres.

Despite a long follow-up time, the confidence intervals are wide due to the size of the study population and the number of events. The trend of the mortality data point in each direction, and the adjusted MI ratios are close to 1.0. We find the results convincing, but further studies including more clinical details and more patients would be appropriate.

Conclusion

Our population-based study, which takes into account differences of gender, age, co-morbidity, previous MI and current coronary interventions, shows that different referral practices for coronary evaluation as an immediate consequence of an abnormal exercise test were not associated with short- or long-term outcome.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgement

This study was supported by a research grant from the West Danish Scientific Committee and the Ringkjoebing County. The National Centre for
Register-based Research is supported financially by the Danish National Research Foundation.

References


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