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Chapter 7

Recurrence and mortality in young women with myocardial infarction or ischaemic stroke: long term follow-up of the RATIO study

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Abstract

**Background:** Little information is available on long term clinical outcome of young patients who survived a cardiovascular event.

**Objective:** To investigate the long term mortality and cardiovascular recurrences in young women who suffered from myocardial infarction or ischaemic stroke.

**Methods:** A cohort began in 1995 and completed in 1997 was followed up to 2012. Participants were young women (<50 years) with either myocardial infarction (n=226) or ischaemic stroke (n=160) or no history of arterial thrombosis (controls, n=782). Incidence rates (IR) and IR ratios (IRR) were calculated for arterial events and mortality during follow-up. Hazard ratios (HR) obtained from Cox proportional models were used to adjust for several cardiovascular risk factors. To determine whether hypercoagulability affects the risk or recurrence, a coagulation score based on procoagulant markers was compiled and used in a quartile analysis.

**Results:** During a median follow-up of 19 years, 83 deaths occurred. Mortality rates per 1000 person-years were 8.8 (95% Confidence Interval (CI) 6.2-12.3) in myocardial infarction patients, 4.4 (95% CI 2.4-7.6) in ischaemic stroke patients, and 2.4 (95% CI 1.7-3.4) in controls. Cardiovascular events occurred in 44 myocardial infarction patients, 37 ischaemic stroke patients and 13 controls, leading to IR per 1000 person-year of 12.1 (95% CI 8.7-16.2), 14.1 (95% CI 9.9-19.4) and 0.9 (95% CI 0.5-1.5), respectively. Adjusted HRs for cardiovascular events were 9.8 (95% CI, 5.0-19.4) in myocardial infarction cases and 12.9 (95% CI, 6.7-25.0) in ischaemic stroke cases compared with controls. A moderate relationship between the coagulation score and cardiovascular recurrences was observed in ischaemic stroke patients but not in myocardial infarction patients.

**Conclusions:** Patients who survived a myocardial infarction or ischaemic stroke at a young age have a high long term mortality and risk of recurrence. An increased coagulation tendency seems to play a role on the recurrences of ischaemic stroke but not of myocardial infarction. These findings provide a direct insight in the consequences of cardiovascular diseases in young women, which persist for decades after the initial event.
Introduction

The rates of death attributable to acute cardiovascular events have declined in the last decades, but the burden of the disease remains high in the increasing number of survivors. This might be particularly important for those affected at a young age, in whom the impact on quality of life and on socioeconomic costs, considering their life expectancy, is the highest. Recent evidence showed that despite a better short-term prognosis in young patients, the long term mortality is unexpectedly high when compared with the elderly; nevertheless, only limited data exist on long-term follow-up in this age category.

Research into myocardial infarction and ischaemic stroke have traditionally focused on male and aging populations, leaving women and the young underrepresented in cardiovascular research. Therefore, knowledge on young onset cardiovascular disease is limited and it is unknown to what extent the results of the studies that include elderly males are applicable to women and the young. Second, age-related risk factors are highly prevalent in elderly patients groups and could obscure the effects of non-age-related risk factors. This makes studies focused on patients with a young age of onset more suitable to study non age-related risk factors.

Of those risk factors, many are shared by both myocardial infarction and ischaemic stroke, whereas there is emerging evidence that others are not. Previous research in young onset disease demonstrated that an increased clotting propensity is a risk factor for ischaemic stroke, whereas the risk of myocardial infarction is only affected marginally. The difference in the role of coagulation in the aetiology of myocardial infarction and ischaemic stroke might also be relevant for the recurrence and prevention of these two diseases, and raises the question whether secondary prevention for ischaemic stroke and myocardial infarction should differ more than it does now.

In this study we determined long term mortality and morbidity in young women who survived myocardial infarction or ischaemic stroke compared with a control group. Moreover, we assessed the impact of known cardiovascular risk factors and of an increased coagulation propensity on the risk of recurrent arterial thrombotic events.
Methods

Patients

Subjects who participated in the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) case-control study form the basis of the RATIO follow-up study. For the present study two groups of patients (subjects who survived either a myocardial infarction or an ischaemic stroke) and controls (subjects without an arterial thrombotic event) were included. Patient selection within the RATIO case-control study has been described in detail previously. In short, all women 18 to 50 years of age who presented with a first event of myocardial infarction or ischaemic stroke (index events) to one of the 16 participating hospitals in the Netherlands between 1990 and 1995 were eligible and approached for study participation. Diagnosis was made on the basis of clinical symptoms and confirmed by appropriate tests. Myocardial infarction was diagnosed by the presence of clinical symptoms, elevated cardiac enzyme levels, and corresponding electrocardiographic changes. Clinical symptoms of ischaemic stroke were confirmed by either computed tomography or magnetic resonance imaging. Ischaemic stroke of cardioembolic origin was excluded by the presence of atrial fibrillation or suggestive cardiac ultrasound imaging. All cases were included from 1995 to 1998. Women were approached to participate as a control subject by random digit dialling and were matched according to age, area of residence, and year of event. A standardized questionnaire on patient characteristics and possible cardiovascular risk factors such as familial medical history, hypertension, diabetes, hypercholesterolemia, and smoking habits was filled in by both cases and controls. Some of these questions were targeted to the year before diagnosis (cases) or the matched index year (controls). All participants were requested to donate blood or buccal swab for DNA analyses. Blood draw procedures and laboratory procedures are described in details in the previous publications. Blood samples, together with a questionnaire on patient characteristics, were collected after a median of 69 months (range, 38 to 117 months) for myocardial infarction cases and 95 months (range, 23 to 146 months) for ischaemic stroke cases, thereby ensuring blood was drawn after the acute phase. All participants gave informed consent and the study was approved by the ethics committees of the participating hospitals.
Follow-up data

In 2013, data on participants of the RATIO case-control study were linked to the Dutch Registry of death certificates and to the Dutch Hospital Data registry by the Central Bureau of Statistics of the Netherlands. The first provides both primary and secondary causes of deaths coded according to The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) classification. The second provides nationwide electronic coverage of data on all hospital admissions since 1995. Data are collected in virtually all general and university hospitals and most specialized clinics. For each hospital admission, information on the date of admission and discharge, diagnoses, and surgical procedures is available. These diagnoses are encoded according to ICD 9th Revision (ICD-9). A previous study comparing a random sample of hospital admissions in the Dutch Hospital Data registry to information from hospital records showed that 99% of the personal (age, sex, date of birth and postal code) and administrative data (date of admission, discharge and death) and 84% of principal diagnoses were correctly encoded. For myocardial infarction, the percentage of correctly encoded diagnosis has since been found to be almost 100%.

Participants of the RATIO case-control study were linked to this registry through date of birth, sex, and postal code. Individuals with information leading to more than one person (e.g., twins or individuals with the same date of birth in the same postal area) or to nobody at all, were excluded.

Outcomes

After linkage to the to the Dutch Registry of death certificates and to the Dutch Hospital Data registry, death, class of death and any further acute arterial thrombotic event were identified. For this study prespecified outcomes were 1) overall mortality and 2) the first occurrence of an acute cardiovascular event, either myocardial infarction or ischaemic stroke, whichever occurred first. Cardiovascular events were further analysed separately as the first occurrence of myocardial infarction and the first occurrence of ischaemic stroke. Mortality was classified as vascular (codes ICD-10 I20 to I95) and non-vascular. The outcome myocardial infarction includes the diagnoses defined by the ICD-9-CM codes 4100 to 4109 and the cause of death
defined by the ICD-10 code I21. The outcome ischaemic stroke includes the diagnosis defined by the ICD-9-CM codes 433, 4330 to 4333, 4338, 434, 4340, 4341, and 4349 and codes 4350- to 4359 (transient ischaemic stroke), and the cause of death defined by the ICD-10 codes I63 and I64. We chose to include these two acute cardiovascular diseases only, as these will invariably lead to hospitalization and were therefore likely to be captured by the Dutch Hospital Data registry.

**Statistical Analyses**

Rates of the prespecified outcomes were measured by dividing the number of events by the observation time, which was defined as the time between the index date and the end of follow-up. Follow-up ended on the date of a first incident cardiovascular event, the date of death, or 31st December 2012, whichever came first. Median follow-up was calculated using the estimates of the censoring distribution for overall mortality. The crude incidence rates (IR) and their 95% confidence intervals (CI) were based on a Poisson distribution and expressed per 1000 persons-years at risk. Kaplan-Meier curves were used to plot the survival for patients and controls subjects. The relative risk of cardiovascular event for patients vs control subjects was estimated by hazard ratios (HR) and corresponding 95% CI with a Cox proportional hazard model. Potential sources of confounding, i.e., age, sex, body mass index (BMI), alcohol consumption, smoking history, diabetes mellitus, hypertension, hyperlipidaemia and family history of a cardiovascular event (i.e., any acute cardiovascular event before 60 years old in a first relative) were included as covariables.

**Coagulation score**

To explore the influence of an increased coagulation propensity on the risk of a recurrent cardiovascular event we compiled an individual prothrombotic score (coagulation score). The score was constructed with coagulation markers measured in both patient groups and in control subjects, being: 1) tissue factor/tissue plasminogen activator induced clot-lysis time (CLT) as a measure of fibrinolytic potential 11; 2) antigen levels of coagulation factors of the intrinsic coagulation system (factor XII, FXII, and FXI and prekallikrein) 18; 3) inhibitor complexes of the serine proteases of the intrinsic coagulation system (C1 esterase inhibitor
for FXIIa, FXIa, Kallikrein, and antitrypsin inhibitor) as measures of the activation of intrinsic coagulation factors; 4) a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS13) antigen levels; 5) von Willebrand factor (VWF) antigen levels; 6) antiphospholipid antibody tests (presence of lupus anticoagulant detected with dilute Russell’s viper venom time (dRVVT) reagents, IgG anticardiolipin antibody concentrations, IgG anti-β2-glycoprotein I concentrations and anti-prothrombin antibodies concentrations); 7) presence of factor V Leiden (either heterozygous or homozygous); 8) presence of G20210A mutation in the prothrombin gene (either heterozygous or homozygous); 9) presence of the homozygous form of the methylenetetrahydrofolate reductase (MTHFR) C677T. The score was based on the beta coefficients, adjusted for matching variables, obtained from logistic regression models for the association between each coagulation marker and index ischaemic stroke. These analyses were based on dichotomous exposures, with the 90th percentile of the control group distribution as cut off value, or on the presence of the genetic variant, or on the test positivity, whichever was the most appropriate. These beta coefficients were summed so that the compiled score represents the coagulation weighted prothrombotic potential for each patients, with higher values of the score corresponding to a higher levels of thrombotic propensity.

To investigate if high values of the coagulation score increased the risk of a recurrent event, we applied a Cox proportional hazard model based on the quartiles of the prothrombotic score distribution as exposure categories, with the lowest quartile as reference. The model was adjusted for age, sex, BMI, alcohol consumption, smoking history, diabetes mellitus, hypertension, hyperlipidaemia and family history of a cardiovascular event.
Results

1376 women (248 myocardial infarction cases, 203 ischaemic stroke cases and 925 controls) participated into the RATIO case-control study. Of these women, 1168 (87%) were successfully linked to the registries (Figure 1). The follow-up therefore included 226 patients with myocardial infarction, 160 patients with ischaemic stroke and 782 control subjects. Median follow-up was 18.7 years (IQR 17.5-20.5).

Figure 1. Flow chart for study participants.

![Flow chart for study participants](image)

RATIO, Risk of Arterial Thrombosis in Relation to Oral Contraceptives.
Recurrence and mortality in arterial thrombosis

Table 1. Baseline characteristics for patients and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Myocardial infarction n=226</th>
<th>Ischaemic stroke n=160</th>
<th>Control group n=782</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at the event (SD)</td>
<td>42.4 (6.1)</td>
<td>40.0 (7.5)</td>
<td>48.4 (7.9)</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>27.1 (5.4)</td>
<td>25.5 (5.7)</td>
<td>24.3 (4)</td>
</tr>
<tr>
<td>Median follow-up (years) (IQR)</td>
<td>18.6 (17.2-20.1)</td>
<td>18.9 (17.3-20.7)</td>
<td>18.7 (17.5-20.5)</td>
</tr>
<tr>
<td><strong>History of, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (5%)</td>
<td>9 (6%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56 (25%)</td>
<td>41 (26%)</td>
<td>48 (6%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>25 (11%)</td>
<td>9 (6%)</td>
<td>20 (3%)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>138 (61%)</td>
<td>90 (57%)</td>
<td>532 (69%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>188 (83%)</td>
<td>100 (63%)</td>
<td>333 (43%)</td>
</tr>
<tr>
<td>Cardiovascular family history*</td>
<td>145 (66%)</td>
<td>82 (56%)</td>
<td>269 (37%)</td>
</tr>
</tbody>
</table>

* Data available for 97% of the subjects in the myocardial infarction group, 92% of the subjects in the ischaemic stroke group, and 94% of the subjects in the control group. SD, standard deviation; IQR, interquartile range.

Clinical characteristics of patients and control subjects at the start of follow-up are depicted in Table 1. Mean age was 44 years, and was similar between patients subgroups. Both myocardial infarction and ischaemic stroke patients had a markedly higher prevalence of traditional cardiovascular risk factors than control subjects. The coagulation score could be calculated for 197 patients with myocardial infarction and 107 patients with ischaemic stroke, for whom blood was available (Figure 1). Mean values of the score were 1.08 (min -0.36, max 5.73) in patients with myocardial infarction and 2.06 (min -0.28, max 9.03) in patients with ischaemic stroke.
Figure 2. Kaplan-Meier curves for overall mortality.

The dashed line represents women with myocardial infarction, the dotted line represents women with ischaemic stroke and the solid line represents controls.

Mortality

During follow-up, 35 (16%) patients with myocardial infarction, 13 (8%) patients with ischaemic stroke, and 35 (6%) control subjects died, leading to a mortality rate per 1000 person-year of 8.8 (95% CI 6.2-12.3) in the myocardial infarction group, 4.4 (95% CI 2.4-7.6) in the ischaemic stroke group, and 2.4 (95% CI 1.7-3.4) in the control group (Table 2). The risk of death was almost 4 times higher for patients with myocardial infarction (IRR 3.7, 95% CI 2.5-5.4) and two times higher for patients with ischaemic stroke (IRR 1.8, 95% CI 1.0-3.5) than for control subjects. Figure 2 shows Kaplan Meier curves for cumulative mortality in all three groups.
Recurrence and mortality in arterial thrombosis

Table 2. Incidence rates for overall mortality and vascular mortality for patients and control subjects.

<table>
<thead>
<tr>
<th>Outcome Events</th>
<th>Incidence rate per 1000 py (95% CI)</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: overall mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction n=226</td>
<td>35 (16%)</td>
<td>3959</td>
</tr>
<tr>
<td>Ischaemic stroke n=160</td>
<td>13 (8%)</td>
<td>2928</td>
</tr>
<tr>
<td>Control group n=782</td>
<td>35 (6%)</td>
<td>14436</td>
</tr>
<tr>
<td><strong>Outcome: vascular mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction n=226</td>
<td>14 (6%)</td>
<td>3959</td>
</tr>
<tr>
<td>Ischaemic stroke n=160</td>
<td>6 (4%)</td>
<td>2928</td>
</tr>
<tr>
<td>Control group n=782</td>
<td>4 (1%)</td>
<td>14436</td>
</tr>
</tbody>
</table>

Overall mortality includes deaths from any cause, whereas vascular mortality includes only deaths from an acute vascular event. Total persons-year depends on the analysis. Incident rate ratios are not adjusted. CI, confidence interval; py, persons-year; ref, reference.

In patients, almost one in two deaths were related to a recurrent vascular event (15/35 for patients with myocardial infarction, leading to a vascular mortality rate of 3.5, 95% CI 1.9-5.9 per 1000 person-year; 6/13 for patients with ischaemic stroke, yielding a vascular mortality rate of 2.1, 95% CI 0.8-4.5 per 1000 person-year), whereas in the control group vascular deaths were less than one seventh of the overall deaths (vascular mortality rate 0.3, 95% CI 0.1-0.7 per 1000 person-year). So, the risk of cardiovascular death was 13 times higher for myocardial infarction patients (IRR 12.8, 95% CI 5.1-32.4) and 7 times higher for ischaemic stroke patients (IRR 7.4, 95% CI 2.6-26.2) than for control subjects.
Incident cardiovascular events

Overall, 94 participants experienced a cardiovascular event during follow-up (either myocardial infarction or ischaemic stroke). 44 patients with myocardial infarction and 37 patients with ischaemic stroke had a recurrent event during follow-up, leading to an incidence rate per 1000 person-year of 12.1 (95% CI 8.7-16.2) and 14.1 (95% CI 9.9-19.4), respectively (Table 3), whereas the incidence rate for cardiovascular event in the control group was 0.9 (95% CI 0.5-1.5). Compared with the control group, myocardial infarction patients had a 12-fold increased risk of a cardiovascular event (age adjusted HR 12.4, 95% CI 6.6-23.1), and ischaemic stroke patients a 15-fold increased risk (age adjusted HR 15.0, 95% CI 7.9-28.1). These relative risks slightly decreased when BMI and a history of alcohol consumption and smoking were taken into account (Table 3). These estimates remained essentially the same upon additional adjustments for chronic diseases such as diabetes, hypertension and hypercholesterolemia, and for a positive family history of cardiovascular disorder.

There was a strong relationship between the type of recurrent event (myocardial infarction or ischaemic stroke) and the index thrombotic event. The incidence rate per 1000 person-years of myocardial infarction during follow-up was higher in myocardial infarction patients (IR 10.1, 95% CI, 7.5-13.8) than in ischaemic stroke patients (IR 2.7, 95% CI, 1.2-5.4) or control subjects (IR 0.4, 95%CI 0.2-0.9). Similarly, incidence rate per 1000 person-years of ischaemic stroke was higher in ischaemic stroke patients (IR 11.1, 95% CI 7.5-15.9) than in myocardial infarction patients (IR 1.9, 95% CI, 0.8-3.8) or control subjects (IR 0.5, 95% CI, 0.2-1.0).
Table 3. Incidence rates and hazard ratios for cardiovascular events.

<table>
<thead>
<tr>
<th>Outcome: any cardiovascular event</th>
<th>Events, n (%)</th>
<th>py</th>
<th>Incidence rate per 1000 py (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR₁ (95% CI)</th>
<th>HR₂ (95% CI)</th>
<th>HR₃ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction n=226</td>
<td>44 (20%)</td>
<td>3654</td>
<td>12.0 (8.7-16.2)</td>
<td>12.4 (6.6-23.1)</td>
<td>10.1 (5.14-19.72)</td>
<td>9.6 (4.9-18.9)</td>
<td>9.8 (5.0-19.4)</td>
</tr>
<tr>
<td>Ischaemic stroke n=160</td>
<td>37 (23%)</td>
<td>2627</td>
<td>14.1 (9.9-19.4)</td>
<td>15.0 (7.9-28.2)</td>
<td>13.3 (10.0-25.3)</td>
<td>12.8 (6.6-24.7)</td>
<td>13.0 (6.7-25.0)</td>
</tr>
<tr>
<td>Control group n=782</td>
<td>13 (2%)</td>
<td>14557</td>
<td>0.9 (0.5-1.5)</td>
<td>ref</td>
<td>ref</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: myocardial infarction</th>
<th>Events, n (%)</th>
<th>py</th>
<th>Incidence rate per 1000 py (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR₁ (95% CI)</th>
<th>HR₂ (95% CI)</th>
<th>HR₃ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction n=226</td>
<td>37 (16%)</td>
<td>3696</td>
<td>10.0 (7.1-13.1)</td>
<td>22.4 (9.3-53.9)</td>
<td>20.9 (8.1-54.0)</td>
<td>18.5 (7.1-48.0)</td>
<td>19.6 (8.0-51.0)</td>
</tr>
<tr>
<td>Ischaemic stroke n=160</td>
<td>8 (5%)</td>
<td>2941</td>
<td>2.7 (1.2-5.4)</td>
<td>6.5 (2.6-18.7)</td>
<td>6.0 (2.1-17.6)</td>
<td>5.4 (1.8-16.2)</td>
<td>5.6 (1.9-16.8)</td>
</tr>
<tr>
<td>Control group n=782</td>
<td>6 (1%)</td>
<td>14588</td>
<td>0.4 (0.2-0.9)</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: ischaemic stroke</th>
<th>Events, n (%)</th>
<th>py</th>
<th>Incidence rate per 1000 py (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR₁ (95% CI)</th>
<th>HR₂ (95% CI)</th>
<th>HR₃ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction n=226</td>
<td>8 (4%)</td>
<td>4152</td>
<td>1.9 (0.8-3.8)</td>
<td>3.8 (1.4-10.5)</td>
<td>2.8 (1.0-8.3)</td>
<td>2.8 (1.0-8.2)</td>
<td>2.7 (0.9-8.1)</td>
</tr>
<tr>
<td>Ischaemic stroke n=160</td>
<td>30 (19%)</td>
<td>2707</td>
<td>11.1 (7.5-15.8)</td>
<td>21.9 (9.6-49.9)</td>
<td>19.1 (8.3-44.3)</td>
<td>18.2 (7.7-42.8)</td>
<td>17.9 (7.6-42.2)</td>
</tr>
<tr>
<td>Control group n=782</td>
<td>7 (1%)</td>
<td>14601</td>
<td>0.5 (0.2-1.0)</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
</tbody>
</table>

Hazard ratios (HR) are obtained by multivariable Cox regression models and are all adjusted for age. HR₁ are also adjusted for smoking, alcohol consumption and BMI. HR₂ are adjusted for #1 and additionally for history of diabetes, hypertension, and hypercholesterolemia. HR₃ are adjusted for #1 and #2 and additionally for family history of a cardiovascular event. CI, confidence interval; py, persons-year; ref, reference.
Coagulation score

Figure 3 shows the association between quartiles of the coagulation score and the risk of a recurrent cardiovascular event, with the first quartile as reference category. Patients with myocardial infarction and high values of the coagulation score (i.e., high thrombotic propensity) had no increase in the risk of a recurrent event compared with patients with low values of the score (i.e., low thrombotic propensity; fourth quartile vs first quartile HR 0.7, 95% CI, 0.3-1.8).

Figure 3. Hazard ratios for cardiovascular recurrence by quartiles of the coagulation score.

Squares indicate hazard ratios for cardiovascular recurrences in patients with ischaemic stroke by quartile of the coagulation score, whereas triangles indicate hazard ratios for cardiovascular recurrences in patients with myocardial infarction by quartile of the coagulation score. Hazard ratios are obtained by Cox proportional hazard models and are all adjusted for age, smoking, alcohol consumption, BMI, history of diabetes, hypertension, and hypercholesterolemia and family history of a cardiovascular event. Dashed lines indicate 95% confidence interval. The y axis scale is logarithmic. q indicates quartile of the coagulation score. The first quartile (q1) is the reference category.
On the contrary, a doubling of the risk of cardiovascular recurrences was observed in patients with ischaemic stroke and high values of the coagulation score compared with patients with low values (fourth quartile vs first quartile HR 1.9, 95% CI 0.6-6.3), with evidence of a “dose response” relationship (second quartile vs first quartile HR 1.3, 95% CI, 0.3-5.1, and third quartile vs first quartile HR 1.6, 95% CI, 0.5-5.6).
Discussion

In the present study we demonstrated that young women who survived myocardial infarction or ischaemic stroke have a high long term mortality, four times higher for patients with myocardial infarction (IRR 3.7, 95% CI 2.5-5.4) and two times higher for patients with ischaemic stroke (IRR 1.8, 95% CI 1.0-3.5) than control subjects. This high mortality is mainly due to a high incidence of fatal vascular events.

Data on long term mortality in young patients who suffered from an arterial thrombotic event are scarce and in our knowledge this is the study with the longest follow-up and the first comparing directly patients with myocardial infarction, ischaemic stroke and control subjects. The longest follow-up available in literature for young ischaemic stroke patients originated from a Dutch and an Italian cohort (median follow-up 8.3 and 11.7 years respectively), in which mortality rates ranged from 12 to 18 per 1000 persons-year.\textsuperscript{5, 22} Similar mortality rates in young survivors of myocardial infarction have been reported in two USA cohorts (median follow-up 3.7 and 12.7 years).\textsuperscript{23, 24} We found mortality rates slightly lower than the ones reported in those cohorts for both myocardial infarction and ischaemic stroke (mortality rate per 1000 persons-year 8.8, 95% CI, 6.2-12.3 for myocardial infarction and 4.4, 95% CI, 2.4-7.6 for ischaemic stroke). This could have several explanations. First, mortality rates in females after a thrombotic event are expected to be lower than the corresponding rates in males.\textsuperscript{5, 25} Second, because patients enrolled in our study after a median time of 1.5 years from the event, mortality rates might be underestimated due to immortal time bias (i.e., a period of follow-up during which, by design, death cannot occur). Mortality is known to be higher in the first year after a thrombotic event, and then become stable over the following years.\textsuperscript{5} Nevertheless, we found that long term mortality was twice as high in myocardial infarction patients than in ischaemic stroke patients. This difference is unlikely to be explained by immortal time bias, because it should affect both diseases equally, and we believe it may reflect a true difference in long term prognosis between the two diseases. We should note, however, that cardioembolic strokes, that are associated with the worst prognosis among ischaemic stroke subtypes, were excluded from our cohort.\textsuperscript{5}

Despite the difference in mortality rates, cardiovascular recurrence rates were similar between myocardial infarction and ischaemic stroke patients (IR per 1000 person-years 12.1, 95% CI, 8.7-16.2 and 14.1, 95% CI 9.9-19.4 respectively), and were in line with previous
separately published results for ischaemic stroke and myocardial infarction.\textsuperscript{24, 26-28} Myocardial infarction patients had a 12-fold increased risk of any arterial thrombotic event (HR 12.4, 95% CI 6.6-23.1) and ischaemic stroke patients a 15-fold increased risk (HR 15.0, 95% CI 7.9-28.1) compared with the control group. These relative risks attenuated only slightly when modifiable cardiovascular risk factors such as smoking, alcohol consumption and BMI were taken into account, but did not reduce further when chronic diseases such as diabetes, hyperlipidemia or hypertension and family history of cardiovascular diseases were added to the regression model (fully adjusted HRs 9.8, 95% CI, 5.0-19.4 and 12.9, 95% CI 6.7-25.0, respectively). This suggests that even when other classical cardiovascular risk factors are taken into account, the risk of a subsequent vascular event remains high in patients with myocardial infarction or ischaemic stroke at young age compared with the general population. Type of recurrence (cardiac or cerebral) was found to be true to type, i.e., the recurrence risk for cerebrovascular disease was highest in stroke patients, whereas the risk of cardiac events was highest in patients with a myocardial infarction. This finding is supported by other studies that investigated ischaemic stroke and myocardial infarction separately.\textsuperscript{24, 29} Previous studies showed that classical risk factors for the first episode, such as hypertension and hyperlipidaemia, were not associated with recurrences in both stroke and myocardial infarction.\textsuperscript{24, 26} It is well known that the risk profile of a recurrent event generally can be entirely different from that of a first event and that often a risk factor is found to be numerically weaker for a second event than for a first.\textsuperscript{30, 31} Here we investigated if procoagulant status, affects the risk of recurrent cardiovascular events. For this purpose we compiled a coagulation score that included several markers of hypercoagulability, both acquired and inherited. The score was weighted on the risk of the index ischaemic stroke event, because index ischaemic stroke has been shown to be the arterial event in which hypercoagulability plays the greatest role.\textsuperscript{32, 33} In this way, the coagulation score represents the individual prothrombotic propensity. When we analyzed the relationship between the score and recurrence we found that high prothrombotic propensity was associated with the risk of vascular recurrences in ischaemic stroke patients, but not in myocardial infarction patients (HR for the fourth quartile vs the lowest quartile 0.7, 95% CI, 0.3-1.8 in patients with myocardial infarction and 1.9, 95% CI 0.6-6.3 in patients with ischaemic stroke). Although women with ischaemic stroke and an overt cardiac-embolic-source were excluded from this study, all other subtypes were combined as data needed for classification were not
available. This hampers the ability to better elucidate the pathophysiological mechanisms beyond our observation. However, we believe our finding may have clinical relevance, given its possible implications on secondary prevention, especially in the era of the direct oral anticoagulants (inhibitors of factor IIa, and factor Xa), that represent new treatment options to establish a more targeted anticoagulation.

As this is an observational study in which blood samples were collected after the index event, one could argue that levels of procoagulant markers in our study may have been affected by acute-phase reactions. However, we consider it unlikely that the effect of procoagulant markers was a result of the acute-phase because procoagulant markers were obtained at least 1.5 year after the index event for both groups of patients.

Strengths of our study are the long follow-up and the homogeneity of data collection. It was therefore possible to compare the risk of death and recurrences in myocardial infarction patients, ischaemic stroke patients and control subjects.

Some caveats should be made. A possible limitation to our study is that arterial cardiovascular events (both myocardial infarction and ischaemic stroke) were not objectively confirmed, but obtained from the Dutch Hospital Data registry. However, a previous study showed that the percentage of correctly encoded myocardial infarctions in this registry was almost 100%. In addition, although the exact percentage of correctly encoded ischaemic strokes is unknown, it is unlikely that any misclassification in this diagnosis would have occurred differently in our two patient groups and the control group. Another limitation is that, despite the long follow-up, numbers of arterial cardiovascular events in some subgroups were small, leading to imprecision of the estimated rates. Finally, in our study we did not have information on medication use during the follow-up period.

In conclusion, we showed that women who survived from an arterial thrombotic event at young age have a high mortality and morbidity. Mortality was higher for myocardial infarction survivors than ischaemic stroke survivors despite the same risk of vascular recurrences, and was mainly due to a high incidence of fatal vascular event during follow-up. Cardiovascular recurrences were true to type and an increased coagulation tendency played a role on the recurrences in woman with ischaemic stroke but not in women with
myocardial infarction. These findings provide a direct insight in the consequences of cardiovascular diseases in young women, which persist for decades after the initial event.


23. Khawaja FJ, Rihal CS, Lennon RJ, Holmes DR, Prasad A. Temporal trends (over 30 years), clinical
Chapter 7


