Left Ventricular Thrombus and Stroke after Acute Myocardial Infarction

by

Thomas Mooe
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av

Thomas Mooe

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Abstract

Left ventricular thrombus and stroke after acute myocardial infarction

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A left ventricular thrombus develops in approximately 40% of patients following an anterior myocardial infarction. Embolization from these thrombi has been regarded as the most important cause of stroke following a myocardial infarction. The occurrence and characteristics of left ventricular thrombi and stroke after anterior myocardial infarction may, however, have changed after the introduction of aspirin and thrombolytics as standard therapy.

The occurrence of left ventricular thrombi was examined in 99 patients with an acute anterior myocardial infarction, 74 of whom were treated with streptokinase. Thrombi were equally common in the thrombolysis group (46%, 95% confidence interval [CI], 35-57%) as in the non-thrombolysis group (40%, 95% CI, 21-59%). The risk of thrombus formation was related to the degree of left ventricular segmental dysfunction.

Using serial echocardiographic examinations, the formation and resolution of thrombi was found to be highly dynamic. The majority of thrombi diagnosed during the hospital stay had resolved at follow-up one month later, irrespective of treatment with streptokinase or anticoagulants. The development of new thrombi was, however, observed at every follow-up examination interval.

One-hundred-and-twenty-four patients suffering a stroke within 28 days of an acute myocardial infarction were identified in the northern Sweden MONICA stroke registry between 1985 and 1994. The overall event rate of ischemic myocardial infarction-related stroke was 1.07%. The risk of a stroke was highest during the first 5 days after the infarction. Only approximately half the strokes were preceded by an anterior myocardial infarction. In a case-control analysis, atrial fibrillation (chronic or new onset), ST elevation and a history of a previous stroke were found to be independent predictors of stroke. There was a long-term trend towards a lower incidence and event rate for myocardial infarction-related stroke.

Clinical stroke characteristics were examined in 103 patients with a first-ever stroke within 28 days of a myocardial infarction and compared with stroke characteristics in 206 control subjects without a recent myocardial infarction. The sudden onset of neurological symptoms, an impairment of consciousness, a progression in neurological deficits and a stroke of the total anterior circulation infarction subclass were more common in cases than in controls. The risk of a recurrent stroke during one year of follow-up was not influenced by a recent myocardial infarction, but patients who had suffered a myocardial infarction had markedly higher mortality.

To conclude, thrombolytic treatment does not reduce the occurrence of left ventricular thrombi after a myocardial infarction. The risk of thrombus formation is related to the extent of the myocardial injury. The development and resolution of thrombi is a highly dynamic process. There is a long-term trend towards a lower incidence and event rate of ischemic stroke after a myocardial infarction. Although the clinical stroke characteristics differ, they are not specific enough to differentiate between patients with and without a recent myocardial infarction.

Key words: myocardial infarction; thrombolytic therapy; left ventricular thrombosis; risk factors; cerebral embolism and thrombosis
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Abstract

Left ventricular thrombus and stroke after acute myocardial infarction

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The occurrence of left ventricular thrombi was examined in 99 patients with an acute anterior myocardial infarction, 74 of whom were treated with streptokinase. Thrombi were equally common in the thrombolysis group (46%, 95% confidence interval [CI], 35-57%) as in the non-thrombolysis group (40%, 95% CI, 21-59%). The risk of thrombus formation was related to the degree of left ventricular segmental dysfunction.

Using serial echocardiographic examinations, the formation and resolution of thrombi was found to be highly dynamic. The majority of thrombi diagnosed during the hospital stay had resolved at follow-up one month later, irrespective of treatment with streptokinase or anticoagulants. The development of new thrombi was, however, observed at every follow-up examination interval.

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To conclude, thrombolytic treatment does not reduce the occurrence of left ventricular thrombi after a myocardial infarction. The risk of thrombus formation is related to the extent of the myocardial injury. The development and resolution of thrombi is a highly dynamic process. There is a long-term trend towards a lower incidence and event rate of ischemic stroke after a myocardial infarction. Although the clinical stroke characteristics differ, they are not specific enough to differentiate between patients with and without a recent myocardial infarction.

Key words: myocardial infarction; thrombolytic therapy; left ventricular thrombosis; risk factors; cerebral embolism and thrombosis
Sammanfattning

Efter en infarkt inom hjärtats framvägg utvecklas en blodpropp (tromb) i vänster hjärtkammare hos cirka 40% av patienterna. Delar av tromben kan lossna (embolisera) och följa med blodströmmen ut i kroppen. Dessa trombfragment kan fastna i mindre blodkärl, t.ex. i hjärnan, och hindra blodcirkulationen. Embolisering från en vänsterkammar-tromb har ansetts vara den vanligaste orsaken till slaganfall (stroke) efter en hjärtinfarkt.

Vid behandlingen av hjärtinfarkt tillförs numera medel som löser upp den kransklärs-propp som orsakat hjärtinfarkten (trombolys), samt medel som förhindrar ny propp-bildning (acetylsalicylsyra, aspirin). Denna behandlingsrutin kan ha påverkat förutsättningarna både för bildning av vänsterkamartromb och för stroke efter hjärtinfarkt.

Förekomsten av vänsterkamartromb undersöktes hos 99 patienter med framväggsinfarkt, av vilka 74 fick behandling med trombolys. Tromb-bildning sågs lika ofta hos behandlade (46%) som hos ej behandlade (40%). Däremot ökade risken för bildning av tromb med hjärtmuskelskadans storlek.


Dessa fynd belyser dynamiken hos vänsterkammar-tromber. Vidare ifrågasätter resultaten betydelsen av framväggsinfarkt som riskfaktor för stroke och talar för att andra mekanismer än embolisering från vänsterkammartromb är viktiga.
This thesis is based on the following papers, which will be referred to by their Roman numerals.


1 Introduction

One of the first observations of intraventricular mural thrombi was made at the beginning of the 19th century (1). It was, however, not until the pathology of myocardial infarction was better understood in the 1920s and 1930s that larger autopsy studies were reported (2). Emboli were commonly encountered in patients with mural thrombi and anticoagulants were therefore introduced in the 1940s in an attempt to deal with this problem (3). Invasive angiographic methods for cardiac examination became generally available in the 1960s. The first report on the angiographic characteristics of left ventricular thrombi appeared in 1974 (4). The introduction of two-dimensional echocardiography in the 1970s made the non-invasive diagnosis and characterization of left ventricular thrombi possible (5).

Several investigators reported that the risk of a subsequent stroke increased if a left ventricular thrombus was present and recommendations for anticoagulant treatment following myocardial infarction were presented (6-8).

The "thrombolytic era", with the introduction of thrombolytics and aspirin as routine treatment in acute myocardial infarction, made it necessary to re-evaluate previous findings relating to the occurrence and embolic risk of left ventricular thrombi.

In the following sections, the current understanding of left ventricular thrombi and stroke after an acute myocardial infarction will be reviewed.
2 Left ventricular thrombus

2.1 Diagnosis

A left ventricular thrombus may develop in a variety of cardiac diseases, but it is usually found in association with a myocardial infarction (9-11). Until the 1970s, all studies of mural thrombi of the heart were based on post-mortem findings. Since then, however, several imaging techniques have become available: angiography (ventriculography), echocardiography, scintigraphy, computed tomography and magnetic resonance imaging.

2.1.1 Ventriculography

The first report of left ventricular thrombi following myocardial infarction, identified by angiography, comprised 22 patients (4). Verification by surgery or autopsy was, however, only obtained in eight patients. Subsequent studies have shown that angiography has a low sensitivity (26-62%) and a low predictive accuracy (54%) for left ventricular thrombi (12-14). Thrombi are often laminated against the ventricular wall, thereby making them difficult to visualize. On the other hand, contrast filling defects may lead to overdiagnosis (15, 16).

2.1.2 Echocardiography

The ability to identify left ventricular thrombi after a myocardial infarction using two-dimensional echocardiography was demonstrated at an early stage (5, 17-19) and the echocardiographic appearance can be described in detail (20). Careful evaluation of spurious intracavitary echoes can reduce the risk of a false positive diagnosis (20, 21).

The diagnostic accuracy of two-dimensional echocardiography, using surgery or autopsy as reference methods, has been examined by several investigators, Table 1 (14, 22-27). The sensitivity was 77-100% and the specificity was 86-100%.

Transesophageal echocardiography is comparable to the transthoracic approach but has higher accuracy when it comes to detecting other potential cardiac sources of emboli (28).
Table 1. Accuracy of echocardiography for the diagnosis of left ventricular thrombi

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Pos pred value</th>
<th>Neg pred value</th>
<th>Validation</th>
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<tr>
<td>Ezekowitz</td>
<td>22</td>
<td>71% (10/13)</td>
<td>96% (26/27)</td>
<td>91% (10/11)</td>
<td>90% (26/29)</td>
<td>Surgery</td>
</tr>
<tr>
<td>Stratton</td>
<td>23</td>
<td>95% (21/22)</td>
<td>86% (48/56)</td>
<td>72% (21/29)</td>
<td>98% (48/49)</td>
<td>Surgery/autopsy/platelet scan</td>
</tr>
<tr>
<td>Visser</td>
<td>24</td>
<td>92% (24/26)</td>
<td>88% (36/41)</td>
<td>83% (24/29)</td>
<td>95% (36/38)</td>
<td>Surgery/autopsy</td>
</tr>
<tr>
<td>Starling</td>
<td>14</td>
<td>77% (10/13)</td>
<td>100% (8/8)</td>
<td>100% (10/10)</td>
<td>73% (8/11)</td>
<td>Surgery/autopsy</td>
</tr>
<tr>
<td>Takamoto</td>
<td>25</td>
<td>83% (10/12)</td>
<td>88% (22/25)</td>
<td>77% (10/13)</td>
<td>92% (22/24)</td>
<td>Surgery</td>
</tr>
<tr>
<td>Sheiban</td>
<td>26</td>
<td>100% (14/14)</td>
<td>97% (61/63)</td>
<td>88% (14/16)</td>
<td>100% (61/61)</td>
<td>Surgery</td>
</tr>
<tr>
<td>Egeblad</td>
<td>27</td>
<td>77% (17/22)</td>
<td>97% (76/78)</td>
<td>89% (17/19)</td>
<td>94% (76/81)</td>
<td>Surgery/autopsy</td>
</tr>
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2.1.3 Platelet scintigraphy
Indium-111 labelled platelets have been used to identify left ventricular thrombi and to examine platelet deposition following an acute myocardial infarction (22, 29, 30). With anatomical verification, a sensitivity of 71% and a specificity of 100% were obtained (22). The method is, however, complicated, expensive and not readily available.

2.1.4 Computed tomography and magnetic resonance imaging
Modern magnetic resonance imaging and computed tomography systems generate high-resolution images of the heart (31, 32). Chronic left ventricular thrombi and other cardiac masses are diagnosed with high accuracy (32-35). Systematic studies during the acute phase of myocardial infarction have, however, not been conducted.

2.1.5 Conclusions
Transthoracic two-dimensional echocardiography remains the method of choice for the identification of left ventricular thrombi. It is readily available, has a low cost and is non-invasive. Alternative techniques include transesophageal echocardiography, computed tomography, magnetic resonance imaging and platelet scintigraphy, all of which may play a complementary role when transthoracic echocardiographic imaging is inconclusive.

2.2 Left ventricular thrombus complicating a myocardial infarction

2.2.1 Autopsy
In a review of eight studies, the incidence of ventricular mural thrombi (left- or right-sided) after myocardial infarction was 44.0% (410/924) (3). Similar findings were reported in a single large autopsy study (42%, 153/366) and the incidence increased with age (36). Mural thrombi commonly occur in the left ventricle (88%, 135/153) (2) and, in one study, the incidence of left ventricular thrombi after an acute myocardial infarction was 37% (37/100), while the incidence in subjects with a healed myocardial infarction was 24% (28/117) (37).

2.2.2 Echocardiography
The reported incidence of left ventricular thrombi following an anterior myocardial infarction ranges from 27% to 57% (38-51). The incidence is related to the number of examinations during the post-infarction period (48). Of all diagnosed thrombi, 0-27% were found within 24 hours, 24-56% within
48 hours, 60-71% within 3 days and 72-80% within one week (43, 44, 46-48). The reported incidence of left ventricular thrombi following non-anterior myocardial infarction was 0% to 11% (38, 39, 41-43, 45, 46, 49). The overall incidence in these studies was 3% (13/431).

2.2.3 Ventriculography
An incidence of left ventricular thrombi of 46% (35/77) in anteriorly located infarctions was observed in one study when the examination was undertaken 5-31 days after the infarction (52).

2.2.4 Methodological considerations
Several aspects need to be considered when different studies of the occurrence of left ventricular thrombi after myocardial infarction are assessed. The most important are patient selection, the imaging technique, the time interval between infarction and examination, the use of serial examinations and whether anticoagulant therapy has been used. Differences in these aspects may explain the fairly wide range of reported thrombus incidence.

2.2.5 Morphology of left ventricular thrombi
A ventricular thrombus may be mural (with a concave free margin following the curvature of the ventricular wall) or protruding (with a curvature opposite to that of the ventricular wall, projecting into the ventricle). A protruding thrombus may also be mobile. The proportion of mural thrombi in patients who were not given thrombolytic therapy ranges between 42-53% (44, 46, 47). Heparin may increase the proportion of thrombi with a mural morphology (53).

2.2.6 Risk factors and prediction
The more extensive the myocardial damage, the higher the risk of left ventricular thrombus formation. Moreover, apical dysfunction is seen in almost every patient with a thrombus (38-41, 43-45, 47-59). As might be expected from these findings, an occluded left anterior descending coronary artery is associated with a high occurrence of thrombus (52, 59). In clinical terms, congestive heart failure is common in patients with a thrombus, reflecting an extensive infarction (43, 44, 47, 52).

Treatment with beta blockers has also been associated with a higher occurrence (60, 61). In the only randomized study, however, patients treated with beta blockers had a worse apical segmental function compared with control subjects (60). Furthermore, two other investigators did not find any
association between the use of beta blockers and thrombus occurrence (52, 53).

The electrocardiogram may indicate an increased risk of developing a thrombus. Persistent ST-segment elevation and positive T-waves, i.e. changes which have been suggested to indicate aneurysm formation, thus have a positive predictive value of 71% (62).

Doppler left ventricular flow pattern can also be used to estimate the risk of thrombus development (63, 64). A positive predictive value of 63% and a negative predictive value of 99% have been reported (64).

2.2.7 Prognosis
The early occurrence of a left ventricular thrombus has been associated with high in-hospital mortality, ranging between 43% (17/40) and 91% (10/11) (44, 48). In one study, however, patients with a thrombus had lower in-hospital mortality and a better functional class after one year of follow-up compared with patients without a thrombus (46, 65). This study differs from most others in that the size of the myocardial infarction was similar in patients with and without a thrombus.

2.2.8 Dynamics of left ventricular thrombi
When two or more serial echocardiographic examinations are performed, it is possible to assess the appearance and resolution of thrombi between the examinations. In several studies of patients with an acute anterior myocardial infarction, performed before the thrombolytic era, the spontaneous resolution of thrombi has been reported (20, 42, 44, 46, 47, 49). In overall terms, 41% (29/71) of the thrombi resolved without anticoagulant treatment during 6-12 months of follow-up. The spontaneous resolution of thrombi during the hospital stay was observed in one study (10%, 2/20) (47).

Only a few studies examining the effect of thrombolytic therapy on the occurrence of left ventricular thrombi in acute myocardial infarction have used serial echocardiography (53, 54, 56) and data on the frequency of spontaneous thrombus resolution without anticoagulant treatment is very limited.
2.3 Risk of a stroke in patients with a left ventricular thrombus

2.3.1 Studies before the thrombolytic era
In an autopsy study of 160 patients with a recent or remote myocardial infarction, 8.8% (14/160) had a cerebral infarction (3). Three of the cerebral infarctions were found in patients who had a left ventricular thrombus (3/65, 4.6%), while 11 were found in those without thrombus (11/95, 11.6%). The author concludes that local thrombus formation may occur secondary to a change in coagulability and decreased blood flow in cases in which the heart does not appear to serve as a source of emboli.

The occurrence of stroke is reported in several echocardiographic studies of left ventricular thrombi following acute anterior myocardial infarction (38-46, 48, 61, 66-69). The duration of follow-up ranged from the hospital stay (41, 67, 68) to 48 months (48). In some studies, anticoagulants were routinely used (38, 39, 41, 43, 45, 69), in others they were not (44, 46, 48) and in some they were used at the discretion of the attending physician (40, 42). Some were randomized studies of prophylactic anticoagulant therapy (61, 66-68). The incidence of stroke varied widely in these studies, ranging from 0% (0/82 patients) (45) to 9.3% (14/150 patients) (69), probably reflecting differences in patient selection. Aspirin was usually not given in these studies.

In overall terms, 44 strokes occurred in 1144 patients with an anterior myocardial infarction (3.8%). A left ventricular thrombus was diagnosed in 393 patients and 31 of them suffered a stroke (7.9%) compared with 13 of 751 patients (1.7%) without a thrombus. Anticoagulants were given to 21/44 (48%) of the patients before the stroke occurred and 16/27 (59%) patients with a left ventricular thrombus were being treated with anticoagulants when the stroke occurred.

These studies were not designed to examine the prevention of stroke by anticoagulants. However, many strokes obviously occur in spite of anticoagulant treatment, irrespective of the presence or absence of a ventricular thrombus.

Whether or not the morphology of the thrombus is an important risk factor for stroke has been examined by several authors (69-77). In retrospective studies, there was an increased risk of stroke when the thrombus was protruding or mobile or had specific grey-scale characteristics (70-73, 76). One major drawback of these studies is their retrospective design. An analysis of the characteristics of a thrombus after the occurrence of an assumed embolic event cannot reliably establish the prospective risk of embolization.
Patients with left ventricular thrombi were followed up prospectively in one study and the risk of embolism was compared with control subjects who did not have a thrombus (74). However, only 19/85 patients with a thrombus had had a recent (< 1 month) myocardial infarction. Furthermore, previous embolic events were more common in the cases than in the controls. Patients with a thrombus ran an increased risk of embolism and the protrusion or mobility (or both) of the thrombus were risk factors for embolization. Because of the study design, these results must be interpreted with caution and are not readily applicable to patients with an acute myocardial infarction.

In one prospective study of 150 patients with an acute anterior myocardial infarction, 9/15 embolic events were associated with a mobile thrombus in the left ventricle (69). In another study, which specifically investigated the morphological characteristics of and changes in thrombi, 109 patients with an anterior infarction were followed up prospectively (78). Fifty-nine thrombi were diagnosed and spontaneous variations in shape and mobility patterns were common. One of seven embolic events was associated with a mobile thrombus.

Because of important differences and weaknesses in terms of study design, the embolic risk associated with particular left ventricular thrombi shapes is difficult to assess. The mobility of a thrombus is, however, probably associated with an increased embolic risk.

2.3.2 Studies of patients given thrombolytic therapy
Strokes are uncommon in observational studies of left ventricular thrombi in the thrombolytic era. In nine studies, only two strokes occurred in 570 patients (0.4%) with an anterior myocardial infarction treated with thrombolytics (53-58, 79-81). A left ventricular thrombus was diagnosed in 125/570 patients and 1/125 (0.8%) had a stroke. In 160 control patients who were not receiving thrombolytic therapy, three strokes occurred (1.9%). These three strokes occurred in 61 patients with a verified thrombus (4.9%). Two of the three stroke patients were treated with anticoagulants before the stroke and died within 24 hours of stroke onset.

In a recent study, two strokes occurred in 138 patients with large anterior myocardial infarctions (59). However, it was not stated whether or not the two patients with a stroke were being treated with thrombolytics, nor was it reported whether they had had a left ventricular thrombus.

Patients who were given thrombolytics were also treated with intravenous heparin and aspirin in most cases. Control patients were usually treated with aspirin but not with heparin. Most patients were followed up
during the hospital stay, but a longer follow-up period (3-12 months) was reported in some studies (54-56, 80).

Compared with trials before the thrombolytic era, the occurrence of stroke following anterior myocardial infarction was markedly lower (0.7% vs 3.8%), both in patients treated with thrombolytics (0.4% vs 3.8%) and in controls (1.9% vs 3.8%), regardless of thrombus occurrence (with thrombus 2.2% vs 7.9%, without thrombus 0.2% vs 1.7%). The low incidence of stroke in patients treated with thrombolytics may be explained at least in part by patient selection because of non-randomized study designs. The low incidence in control patients is more difficult to attribute to selection mechanisms.

2.4 Prevention of thrombus formation

2.4.1 Heparin and warfarin
Four small randomized studies have evaluated the preventive efficacy of full-dose heparin infusion, started within 12 hours of the onset of infarction (66-68, 82). Treatment was continued with warfarin until discharge (66-68) or with subcutaneous heparin until 20 to 50 days after admission (82). Serial echocardiographic examinations were performed. In one study, a significantly lower incidence of thrombi was observed in treated patients compared with controls (0/26 vs 7/27, p<0.01) (66), while no preventive effect was found in the other three studies. In all four trials, the overall incidence of thrombus was 31% (26/85) vs 43% (41/96) in treated versus controls, a tendency in favour of treatment (p=0.09).

In a large randomized trial comprising 183 patients with an anterior myocardial infarction (61, 83), the subcutaneous administration of 12500 units of heparin every 12 hours prevented the developement of left ventricular thrombi during the first 10 days more effectively than 5000 units every 12 hours given conventionally to prevent venous thrombosis (10/95, 11% vs 28/88, 32%, p=0.0004).

In a large post-infarction study of subcutaneous heparin (12500 units every 12 hours), a subgroup of 200 patients with an anterior myocardial infarction was studied by echocardiography before discharge. A left ventricular thrombus was found in 18% (19/107) of the heparin-treated patients compared with 37% (34/93) of the controls who received no anticoagulants (p<0.01) (84).

These results show that heparin in adequate doses can reduce the occurrence of left ventricular thrombus after myocardial infarction.
2.4.2 Antiplatelet drugs
The incidence of left ventricular thrombi when antiplatelet therapy was given within 12 hours of the onset of a myocardial infarction was examined in two prospective, randomized, placebo-controlled trials (85, 86). In one study, 100 mg of aspirin daily was used, in the other 150 mg of aspirin daily was given in combination with 75 mg of dipyridamol three times daily. Serial echocardiographic examinations were performed for 12 weeks and 10 days of follow-up respectively. The incidence of thrombi in treated versus control subjects in the two trials was 33% (14/45) vs 32% (15/47) and 73% (8/11) vs 33% (3/9). Consequently, antiplatelet therapy does not prevent the development of a thrombus.

2.4.3 Thrombolytics
No randomized study has been performed to examine the effect of thrombolytic therapy on left ventricular thrombus formation. In two non-randomized studies, thrombolytic therapy for acute myocardial infarction did not reduce the occurrence of left ventricular thrombi. The incidence of thrombi in treated versus control patients was 14% (9/65) vs 23% (7/31) and 20% (14/70) vs 14% (13/95) respectively (58, 79). In two other trials, the incidence of thrombi (27% and 28% respectively) was comparable with the incidence in historical controls (53, 81).

In six studies (one using ventriculography), a lower incidence of left ventricular thrombus following thrombolytic therapy was reported (54-57, 59, 87). The incidence in treated versus non-randomized control subjects ranged between 0-26% versus 18-70% respectively. If all the studies are considered together, the incidence in thrombolysed patients was 14% (29/203) versus 46% (102/223) in controls. In the five echocardiographic studies, thrombolysed patients received more aggressive anticoagulant treatment or had better left ventricular function compared with controls.

In one study, a low incidence (9%, 7/76) compared with historical controls was reported (80).

There was no difference in the incidence of thrombus in a randomized study comparing thrombolytic treatment with streptokinase and tissue plasminogen activator (53).

Conflicting results therefore exist when it comes to whether thrombolytic treatment reduces the incidence of left ventricular thrombus after an acute anterior myocardial infarction. In the subgroup of patients with reperfusion of the infarct-related artery, myocardial function was better preserved and the incidence of thrombi was reduced (52, 59).
2.5 Treatment of a left ventricular thrombus

2.5.1 Heparin
Intravenous heparin has been used to treat patients with thrombi who display a high-risk morphology (protruding, mobile, or both) (88). Twenty-three patients were treated with full-dose heparin for 7 to 22 days. There was no control group. Only five patients had had a recent myocardial infarction (within 2 months). The resolution of thrombi was observed in 83% (19/23) of the patients. No embolic event occurred. The lack of a control group and of follow-up examinations after thrombus resolution makes it difficult to assess the benefit of heparin treatment.

In one case report, heparin infusion followed by warfarin was reported to have resolved a very large left ventricular thrombus (89).

2.5.2 Anticoagulants
The effect of anticoagulant therapy on left ventricular thrombus was assessed in a randomized study (90). Thirty-eight patients with a thrombus were included within 5 weeks (mean 4 weeks) following an acute infarction. The resolution of thrombi was seen more frequently in treated patients compared with controls after 3 months, 12/17 vs 2/17, and after 1 year, 15/17 vs 4/17, p<0.001.

2.5.3 Antiplatelet drugs
The in vitro and in vivo behaviour of platelets was studied in eleven patients with left ventricular aneurysms and mural thrombi (91). Five patients on aspirin (300-2400 mg daily) had reduced platelet aggregation in vitro compared with 6 controls. However, in all the treated patients, scintigraphy showed platelet incorporation into the ventricular thrombi. Another study, also using scintigraphy, has shown that sulfinpyrazone (7 patients), aspirin plus dipyridamol (6 patients) and warfarin (4 patients) may all interrupt platelet deposition in some patients with chronic left ventricular thrombi (92). Another scintigraphic study has shown the interruption of platelet deposition by ticlopidine (93).

The number of patients was small in these studies, but it seems unlikely that antiplatelet therapy increases the resolution of thrombi.

2.5.4 Thrombolytics and surgery
In one report on 16 patients with large left ventricular thrombi after myocardial infarction urokinase was given (94). Ten of the thrombi resolved
after two to eight days of treatment without embolic complications. In another report on four patients, however, two embolic complications (one lethal stroke) occurred when a left ventricular thrombus was treated with fibrinolytic therapy (49).

The surgical removal of left ventricular thrombi has been described in a few case reports of patients with recurrent embolism or impending embolization (95, 96). The long-term results are, however, not known.
3 Stroke

3.1 General considerations

The World Health Organization (WHO) definition of stroke is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than a vascular origin" (97). This definition excludes transient ischemic attacks and stroke events caused by infection, tumour and trauma (98, 99).

Stroke is the third most frequent cause of death, after heart disease and cancer, in most industrialised populations (100). Stroke accounts for 10-12% of all the deaths in these countries and about 88% of all the deaths attributed to stroke take place among people aged 65 and over (100). The cause of death is usually progressive stroke or cardiac complications (101, 102). There is a declining trend in stroke mortality, while there is only a modest or no decrease in stroke incidence (103). In Swedish community studies, the annual first-ever stroke incidence per 100000 inhabitants is 208 to 427 (103).

About 80% of all stroke events are ischemic, while approximately 20% are caused by an intracranial hemorrhage (104-107). The cause of ischemic strokes may be atherothrombotic or cardioembolic. Several classifications have been proposed according to pathogenetic mechanism, arterial site or clinical findings (108-112).

After age, the most important risk factors for ischemic stroke are hypertension, smoking and diabetes (113, 114).

3.2 The WHO MONICA Project

At the beginning of the 1980s, the World Health Organization initiated the MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) study. The aim of the study was to relate changes in known risk factors to trends in cerebrovascular and coronary heart disease morbidity and mortality (97, 115, 116). In 1985, northern Sweden entered the study and a MONICA secretariat for stroke was established in Umeå (103).
3.3 Heart disease and stroke

3.3.1 Population-based studies
Atherosclerosis is a generalized or multifocal vascular disease, which commonly co-exists in coronary and cerebral arteries (117). In the Framingham Study, coronary heart disease (myocardial infarction, angina pectoris, congestive heart failure) was related to atherothrombotic brain infarction (118). Left ventricular hypertrophy was associated with a 10-fold, chronic non-rheumatic atrial fibrillation with a 8.5-fold increase in stroke incidence and congestive heart failure with a 9-fold increase. In another population-based study, the cumulative probability of stroke after a diagnosis of angina pectoris was estimated (119). No significant difference was noted between the observed probability of a stroke (5.8%) and the expected probability throughout 10 years of follow-up. The exclusion of myocardial infarction patients and a weak association between the clinical diagnosis of angina pectoris and anatomically verified coronary disease may, however, explain the low observed occurrence of stroke.

3.3.2 Cardiogenic brain embolism
Accurate and safe diagnostic methods to establish a diagnosis of cardioembolic stroke in individual patients are still lacking. The presence of a potential cardioembolic source in the absence of cerebrovascular disease in a patient with non-lacunar stroke remains the mainstay of clinical diagnosis (6, 120, 121), although contradictory findings have been reported (122). The estimated prevalence of presumed cardioembolic stroke will thus depend on the application of diagnostic criteria and on how thoroughly patients are evaluated (123-125). Many sources of cardiogenic embolism have been identified and different levels of evidence supporting cardiogenic brain embolism have been suggested, Tables 2 and 3 (121, 126-128). The percentage of ischemic strokes attributed to cardiogenic embolism ranges between 15% and 30% in clinical studies (120, 121, 124).

3.3.3 Neurological features
Several neurological features of stroke have been suggested as indicating an embolic mechanism, Table 4 (129). However, these features are neither sensitive nor specific indicators of the stroke mechanism. Abrupt stroke onset and diminished consciousness are reported in many patients without potential cardioembolic sources. Seizures and headache do not distinguish cardioembolic
Table 2. Sources of cardiogenic embolism (121)

**Valvular diseases**
- Mitral stenosis*
- Prosthetic valves*
- Infective endocarditis*
- Non-bacterial (marantic) endocarditis*
- Calcific aortic stenosis
- Mitral annulus cacification
- Mitral prolapse

**Acute myocardial infarction***

**Left ventricular thrombus***

**Arrhythmias**
- Atrial fibrillation*
- Sick sinus syndrome*

**Dilated cardiomyopathy***

**Cardiac tumours***

**Paradoxical emboli**
- Atrial septal defects
- Patent foramen ovale
- Ventricular septal defects

**Miscellaneous sources**
- Atrial septal aneurysms
- Iatrogenic causes

*=usually regarded as a major cardioembolic source

Table 3. Levels of evidence supporting cardiogenic brain embolism (121)

**Possible: presence of cardioembolic source**
A: Major risk sources (see Table 2), or
B: Minor risk sources (see Table 2)

**Probable: requires ultrasound and usually computed tomography**
Presence of a cardioembolic source and all the following:
A: Minimal or no (<50% stenosis) carotid artery atherosclerosis by ultrasound and
B: Non-lacunar infarct and
C: No other explanation of stroke and
D: No major cerebrovascular risk factor (hypertension, diabetes)

**Clinically definite: requires arteriography**
Presence of a cardioembolic source and either:
A: embolic occlusion without substantial proximal atherosclerosis, or
B: normal arteriography, no other explanation of stroke and either:
1: non-lacunar infarct, or
2: lacunar infarct without chronic hypertension and diabetes
Table 4. Neurological features suggested to indicate an embolic mechanism (129)

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden onset</td>
</tr>
<tr>
<td>Loss of consciousness at onset</td>
</tr>
<tr>
<td>Seizure at onset</td>
</tr>
<tr>
<td>Headache at onset</td>
</tr>
<tr>
<td>Onset during activity</td>
</tr>
<tr>
<td>Peak of deficit at onset</td>
</tr>
<tr>
<td>Nausea and vomiting at onset</td>
</tr>
<tr>
<td>Evidence of two (or more) separate focal deficits</td>
</tr>
<tr>
<td>Evidence of embolization to other organs</td>
</tr>
</tbody>
</table>

strokes from strokes with other causes (120, 121, 129). A distinct clinical neurological profile indicating embolic stroke has not been identified (129).

3.4 Stroke after a myocardial infarction

3.4.1 Before the thrombolytic era

Autopsy studies in the 1920s and 1930s reported an incidence of cerebrovascular lesions of 1.2% to 6.4% in patients with a myocardial infarction (130). These figures were based on the finding of a coronary occlusion and a cerebral thrombus, but not necessarily clinical symptoms. In two autopsy studies from the 1940s and 1950s, the incidence of a cerebral infarction in cases with a myocardial infarction was 8.8% (14/160) and 9.0% (19/210) respectively (3, 131).

In controlled trials of anticoagulant treatment in acute myocardial infarction, an incidence of cerebrovascular lesions of 1.1% to 3.8% in untreated control subjects has been reported (132-135). Patients with an increased risk of hemorrhagic complications and previous cerebrovascular lesions were usually excluded. The duration of follow-up was approximately one month. The overall occurrence of stroke in these studies was 2.9% (58/1973).

In observational studies of patients treated at coronary care units, the incidence of stroke was 0.8% to 1.9% during the hospital stay (136-139). The overall occurrence of stroke was 1.0% (91/8759). The exclusion criteria were not specified. The higher incidence of cerebrovascular lesions in the autopsy studies may be explained by more advanced disease in fatal cases and the
inclusion of asymptomatic events. The low incidence in reports from coronary care units may be caused by the selection of low risk-patients.

3.4.2 Stroke in the thrombolytic era

3.4.2.1 Streptokinase
The number of stroke events was too low or the stroke data was too incomplete in some trials to permit further analysis of stroke incidence (140, 141). Two large placebo-controlled trials have been performed (142-145). In the GISSI trial, the in-hospital incidence of stroke in the treatment group was 0.84% (49/5860) and 0.68% (40/5852) in the placebo group. Eight hemorrhagic strokes were confirmed after streptokinase, while no hemorrhagic strokes were found among controls. Similar findings were reported in the ISIS-2 trial. The in-hospital incidence of stroke was 0.7% (61/8490) in treated subjects and 0.8% (67/8491) in controls. Seven hemorrhagic strokes were confirmed, all occurring in patients treated with streptokinase. Anticoagulants were not routinely used. In both trials, many of the stroke patients were not examined with computed tomography.

3.4.2.2 Tissue plaminogen activator
In small placebo-controlled trials, the in-hospital incidence of stroke ranged between 2.0% (7/355) and 2.7% (2/73) in the treatment group and between 0.5% (2/366) and 1.4% (1/71) in the control group (146, 147). All these patients received heparin infusions. In the ASSET trial (148, 149), the stroke incidence after one month of follow-up was 1.1% (28/2512) in the treatment group and 1.0% (25/2493) in the control group. All the patients received a heparin infusion during the first day. Seven hemorrhagic strokes were confirmed in the treatment group and two in the control group. In the TIMI phase II trial, patients treated with 150 mg of tissue plasminogen activator had a high occurrence of hemorrhagic stroke (2.1%, 11/520) (150). In the combined TAMI trials, the overall incidence of stroke was 1.8% (13/708), one-third of which (4/708) were hemorrhagic (151).

3.4.2.3 Anisoylated plasminogen streptokinase activator complex (APSAC)
In a placebo-controlled trial, the incidence of stroke or transitory ischemic attacks within 30 days was 1.4% (9/624) in the treatment group and 0.6% (4/634) in the control group (152, 153).
3.4.2.4 Streptokinase versus tissue plasminogen activator
In three large trials, the occurrence of stroke in patients treated with streptokinase or tissue plasminogen activator can be compared, Table 5 (154-156). The stroke incidence was higher in the tissue plasminogen activator groups and this can be attributed to a higher occurrence of cerebral hemorrhages.

Table 5. Incidence of stroke in patients treated with streptokinase (SK) or tissue plasminogen activator (tPA)

<table>
<thead>
<tr>
<th>Ref</th>
<th>SK Cerebral hemorrhage</th>
<th>SK Any stroke</th>
<th>tPA Cerebral hemorrhage</th>
<th>tPA Any stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI-2</td>
<td>0.29%</td>
<td>0.94%</td>
<td>0.42%</td>
<td>1.33%</td>
</tr>
<tr>
<td>ISIS-3</td>
<td>0.24%</td>
<td>1.04%</td>
<td>0.66%</td>
<td>1.39%</td>
</tr>
<tr>
<td>GUSTO</td>
<td>0.49%</td>
<td>1.22%</td>
<td>0.72%</td>
<td>1.55%</td>
</tr>
</tbody>
</table>

3.4.2.5 Comments
In the trials of thrombolytic therapy, many stroke patients were not examined using computed tomography or magnetic resonance imaging. A large proportion of the strokes were therefore not classified as hemorrhagic or ischemic. Furthermore, high-risk patients (e.g. uncontrolled hypertension, previous stroke) were excluded and this probably contributes to the relatively low occurrence of stroke. In the placebo-controlled trials, the overall incidence of stroke was similar in treated and control subjects, while in patients receiving tissue plasminogen activator in particular a large proportion of the strokes were hemorrhagic (157).

3.4.3 Stroke incidence in survivors of a myocardial infarction
In one trial from the 1970s, 260 consecutive survivors of a myocardial infarction were followed-up for 5 years (158). The yearly incidence of stroke was 0.8%. The same stroke incidence was found the first year after discharge in 4808 survivors of myocardial infarction from 13 coronary care units in Israel (0.8%, 37/4808) (159).
In the Multicentre Diltiazem Postinfarction Trial, 2466 patients were randomized from day 3 to day 15 after infarction and followed up for an
average of 25 months. In a retrospective analysis, the yearly stroke incidence was 1.5% (160). The SAVE trial enrolled 2231 patients who had left ventricular dysfunction after an acute myocardial infarction (161). From 3 to 16 days after a myocardial infarction, patients were randomly assigned to receive an ACE inhibitor or placebo. The average follow-up was 42 months and the rate of stroke per year of follow-up was 1.5% (162).

In two trials of long-term anticoagulant treatment after a myocardial infarction, the rate of stroke per year in the placebo groups was 2.4% and 1.2% respectively (163, 164). To conclude, stroke is a relatively rare complication in survivors of myocardial infarction.

3.4.4 Secular trend in stroke incidence
The secular trend in the incidence of stroke after a myocardial infarction is important when considering the cost effectiveness of possible preventive measures. The incidence of stroke complicating a myocardial infarction has seemed to decline for several decades, from approximately 3% in the early trials of anticoagulant treatment to approximately 0.7% in trials of streptokinase treatment. Whether this trend is true or is caused by different investigational biases is, however, difficult to assess (165). The hospital period for myocardial infarction has become shorter, the sensitivity of enzyme assays has increased and the pharmacological treatment of myocardial infarction has changed. All these factors may have played a role in reducing the incidence of stroke during the hospital stay. Furthermore, selection bias in recent thrombolytic trials owing to the exclusion of high-risk patients has probably reduced the risk of stroke.

A population-based study with long-term follow-up may resolve this issue.

3.4.5 Risk factors for stroke after a myocardial infarction
In small studies before the thrombolytic era, a more extensive myocardial infarction (166), atrial fibrillation and a previous stroke (137), plus high fibrinogen levels (166), were associated with an increased risk of stroke. In a large trial, older age (10-year increase, odds ratio 1.49), congestive heart failure (odds ratio 2.74) and a history of stroke (odds ratio 5.33) were independent predictors of stroke (139). Diabetics had a higher frequency of stroke than non-diabetics in one trial (7% versus 3% respectively) (167). No attempt was made to differentiate between ischemic and hemorrhagic strokes in most of these studies. In one study, however, computed tomography was
performed in 74% (14/19) of the stroke patients and no hemorrhage was found (167).

In the GISSI trial, older age and congestive heart failure were predictors of stroke (ischemic and hemorrhagic together) in a multivariate analysis. An anterior-lateral location was associated with a higher risk of stroke than posterior-inferior infarctions (relative risk 1.95), but 18/99 cerebrovascular events were not included in the analysis (168).

In the GISSI-2/International Study Group trials, 74% (174/236) of the strokes were further investigated by computed tomography or autopsy. Older age and congestive heart failure were predictive of ischemic stroke, while female sex and high diastolic blood pressure were predictive of hemorrhagic stroke (169).

The GUSTO trial provides the largest database of hemorrhagic strokes after thrombolytic therapy (156). Advanced age, low weight, prior stroke, a history of hypertension, systolic and diastolic blood pressure and tissue plasminogen activator treatment were independent predictors of intracranial hemorrhage (170).

In the larger trials, an anterior infarct location has not been independently predictive of stroke (139, 169). In three large trials, the proportion of stroke patients with a preceding anterior myocardial infarction was 50% (27/54) (139), 58% (57/99) (144) and 47% (111/236) (169).

During long-term follow-up after a myocardial infarction, conflicting data have been presented on the location of the myocardial infarction and the risk of stroke (160, 171). Large artery disease and risk factors for arterosclerosis are probably important predictors of late stroke after a myocardial infarction (172).

In addition to the clinical characteristics, changes in hemostatic function and platelet aggregability may play an important role in the risk of stroke after a myocardial infarction (173-182).

3.4.6 Primary prevention of stroke after a myocardial infarction

3.4.6.1 Heparin
In the GISSI-2/International Study Group trial, 20891 patients were randomly allocated to subcutaneous heparin (12500 units twice daily) or no heparin in addition to thrombolytic therapy (183). Heparin treatment was continued until hospital discharge. Aspirin (300-325 mg daily) was recommended for all patients. There was no difference in the in-hospital stroke incidence between the groups (heparin 1.1%, 117/10361, no heparin 1.1%, 119/10407). The
incidence of hemorrhagic strokes was also similar (heparin 0.3%, no heparin 0.4%).

The ISIS-3 trial had a similar design (155). Heparin did not reduce the overall stroke incidence up to day 35 (heparin 1.28%, 261/20400, no heparin 1.18%, 240/20375) but was associated with a higher incidence of cerebral hemorrhage (0.56% versus 0.40%, p<0.05).

In the GUSTO trial, 20023 patients were randomly allocated to subcutaneous (12500 units twice daily) or intravenous (bolus 5000 units and infusion 1000 units per hour) heparin in addition to streptokinase (156). Subcutaneous heparin was given for 7 days or until discharge, and intravenous heparin for at least 48 hours. The overall stroke incidence was similar in the two groups (subcutaneous heparin 1.22%, intravenous heparin 1.40%), as was the incidence of hemorrhagic stroke (0.49% versus 0.54%). Heparin has therefore not been shown to reduce the incidence of stroke in patients with a myocardial infarction treated with thrombolytics and aspirin. In patients who were not receiving thrombolysis, no study provides reliable estimates of the effect of heparin on stroke occurrence.

3.4.6.2 Warfarin
A number of randomized trials have suggested that anticoagulant-treatment has a beneficial effect on stroke incidence after an acute myocardial infarction (132, 184-188). Three randomized trials have been performed and two report a statistically-significant reduction in stroke occurrence in patients who were given anticoagulants (133-135). A meta analysis also suggested that anticoagulants were of benefit (157). However, the heterogeneity of the trials makes any interpretation of the effect difficult. Furthermore, all these trials were performed before the introduction of thrombolytics and aspirin as standard therapy for acute myocardial infarction.

Three double-blind, randomized, placebo-controlled trials provide data about the stroke-prevention effect of long-term anticoagulant treatment in survivors of myocardial infarction (163, 164, 189). The mean duration of follow-up ranged between 2 years and 37 months and the relative risk of stroke was reduced by 40% to 55%. The yearly reduction in stroke incidence was 0.9%, 1.3% and 0.5%, while the yearly increase in major bleeding complications was 3.4%, 0.6% and 1.0% respectively.

3.4.6.3 Aspirin
In a meta analysis including all the randomized trials available by March 1990, aspirin significantly reduced the incidence of non-fatal stroke after an acute
myocardial infarction (190). The odds ratio was 0.6, corresponding to a reduction of 40% in the odds of stroke. Nearly all the stroke events in this analysis were recorded in the ISIS-2 trial, in which 17187 patients were allocated randomly to aspirin (162.5 mg daily) or placebo (145). In the aspirin group, the in-hospital stroke incidence was 0.55% (47/8492) compared with 0.95% (81/8489) in the placebo group (p<0.01). In the GISSI-2/International Study Group trials, non-randomized treatment with aspirin (300-325 mg daily) reduced the adjusted odds of stroke by 56% (odds ratio 0.44, 95% confidence interval 0.32-0.61)(169). These data show that aspirin effectively reduces the risk of stroke after an acute myocardial infarction.

3.4.6.4 Aspirin versus anticoagulants
Oral anticoagulant treatment has been compared directly with aspirin in two randomized trials, with inconclusive results (191, 192). The German-Austrian trial randomized 942 patients within 30 to 42 days of acute infarction to aspirin (1.5 g daily), placebo or anticoagulant therapy. The duration of follow-up was 2 years. Stroke incidence was not specifically reported but the number of fatal strokes and other thrombo-embolic events was 1, 7 and 2 among patients treated with aspirin, placebo and anticoagulants respectively. In the EPSIM trial, 1303 patients were randomized a mean of 11.4 days after an acute myocardial infarction to aspirin (0.5 g three times a day) or anticoagulants. The mean duration of follow-up was 29 months. In the aspirin group, three strokes occurred (one hemorrhagic), while five strokes (two hemorrhagic) and two transitory ischemic attacks occurred in the anticoagulant group.

Trials with sample sizes sufficient for the detection of clinically important differences between warfarin and aspirin, using modern treatment regimens, are needed and in progress (193).

3.5 Recurrent thrombo-embolism after "cardioembolic" stroke
In an autopsy study of 300 patients with a myocardial infarction, peripheral embolism was diagnosed in 60 (2). The rate of recurrent embolism was estimated at 30% (18/60) (194), but the rate of recurrent stroke was not specifically reported. In a clinical study of arterial embolism, the rate of recurrent embolic events in patients with a myocardial infarction was 25% (7/28) and 5/7 recurrent episodes occurred within 14 days (195). The proportion of recurrent cerebral embolism was not reported. It has been estimated that about 12% of patients with a cardiogenic embolic stroke will
experience a second brain embolus within two weeks of the initial stroke (6). This estimate is based on a number of small retrospective studies, usually including patients with rheumatic heart disease or atrial fibrillation. In two prospective trials, the number of recurrent stroke events was too low (n=4) to permit conclusions about the risk of recurrent stroke (196).

In a study comprising 1273 patients with a cerebral infarction, 246 had a cardioembolic stroke (197). The proportion of patients with a recent myocardial infarction was, however, not reported. The rate of recurrent stroke within 30 days of the index stroke was 4.3% (10/246). A history of hypertension and the blood sugar concentration at admission were identified as the predominant predictors of early recurrence. Previous small studies appear to have overestimated the risk of recurrent stroke. No large trials have specifically investigated the risk of a recurrent stroke following a recent myocardial infarction.

### 3.6 Secondary prevention of cardioembolic stroke

No randomized trial has assessed the effect of antithrombotic therapy in reducing the rate of recurrent strokes following a recent myocardial infarction. Trials of anticoagulant therapy in patients with assumed cardiogenic embolic brain infarction have been small and inconclusive (196). Furthermore, the hemorrhagic transformation of embolic brain infarction may occur, thereby making the therapeutic considerations even more complex (198, 199).
4.0 Bleeding complications associated with antithrombotic therapy

4.1 Aspirin

Aspirin has been used in two large controlled primary prevention trials (200, 201). In the US Physician health study, 325 mg of aspirin every other day was used to prevent thrombo-embolic events. The yearly incidence of hemorrhagic strokes in treated and control subjects was 0.04% (23/54650 person-years of observation) and 0.02% (12/54636 person-years of observation) respectively (p=0.06). In the British Doctors trial, the incidence of hemorrhagic stroke was similar in those subjects who received 500 mg of aspirin daily (0.016% per year) compared with controls (0.021% per year). The ISIS-2 trial randomly assessed, with placebo control, the effects of oral aspirin (162.5 mg daily) in patients with a suspected acute myocardial infarction (145). The rate of major bleedings was 31/8492 in treated subjects and 33/8489 in controls. In three randomized placebo-controlled trials of aspirin (75 mg, 325 mg and 300 mg daily) in patients with non-valvular atrial fibrillation, the incidence of major or fatal bleedings in cases and controls was 0.2% vs 0%, 1.9% vs 1.8% and 0.9% vs 0.5% per year respectively (202-204). Aspirin in patients with heart disease is therefore safe. The risk of serious hemorrhagic complications is only marginally increased.

4.2 Warfarin

In three randomized, placebo-controlled trials of survivors of myocardial infarction, anticoagulant therapy increased the incidence of serious bleeding by 3.4%, 0.6% and 1.0% per year respectively (163, 164, 189). In two randomized trials, aspirin (0.5 g three times daily in both trials) was compared with anticoagulant therapy in survivors of myocardial infarction (191, 192). In patients treated with anticoagulants, the incidence of serious bleeding increased by 0.5% and 1.0% per year respectively. A review of anticoagulant-related bleeding showed that warfarin increased the frequency of total, major and fatal bleeding in patients with any of four indications for therapy: cerebrovascular disease, ischemic heart disease, hip surgery and atrial fibrillation (205). The average annual frequencies of fatal, major or minor bleeding during warfarin therapy were 0.6%, 3% and 9.6% respectively.
These frequencies are approximately five times those expected without warfarin therapy. In another analysis of recent randomized trials of oral anticoagulants in patients with atrial fibrillation (202-204, 206-208), prosthetic heart valves (209) and in survivors of myocardial infarction (163), the mean incidence of major non-fatal and fatal bleeding was 1.7% (range 0.2% to 5.2%) and 0.5% (range 0% to 1.4%) per year respectively (210). Patients allocated to placebo treatment (seven trials) had a mean incidence of major and fatal bleeding of 0.7% (range 0% to 1.6%) and 0.1% (range 0% to 0.2%) respectively. Compared with previous reports, these data indicate a lower incidence of anticoagulant-related bleeding (211-213). This could be explained by the more accurate control of anticoagulant therapy, lower treatment intensity and the exclusion of patients with risk factors for bleeding in recent prospective trials (210). Several patient-specific risk factors for anticoagulant-related bleeding have been identified and can be used to estimate an individual patient’s risk of major bleeding (205, 214, 215).

4.3 Combined therapy with anticoagulants and aspirin

Several randomized trials have shown that aspirin may increase the risk of bleeding during warfarin therapy in patients with prosthetic heart valves (216, 217). A recent placebo-controlled trial investigated the effect of adding 100 mg of aspirin to warfarin in patients with mechanical heart valves or with tissue valves plus atrial fibrillation or a history of thrombo-embolism (209). The average duration of follow-up was 2.5 years. Bleeding occurred in 35% (71/186) of the patients in the aspirin group as compared with 22% (49/184) of control patients (p=0.02). Minor bleeding occurred in 16.7% versus 10.4%, major non-fatal bleeding in 7.5% versus 5.2% and fatal bleeding in 1.1% versus 1.4% per year in the aspirin versus control group respectively. The number of minor and non-fatal major bleedings therefore increased, while the number of fatal bleedings was too low (3 versus 4) to permit any conclusion about the risk of the combined therapy.

4.4 Heparin

The frequency of bleeding in patients treated with heparin in a dose intended to attain a measurable effect on the activated partial thromboplastin time has been reviewed (205). In eight cohort studies with a total of 937 patients, the average daily frequencies of fatal, major and major or minor bleeding were
0.05%, 0.8% and 2.0% respectively. These frequencies are approximately twice those expected without heparin therapy (218).
5. Aims

The present series of investigations was undertaken to examine whether thrombolytic treatment reduces the occurrence of left ventricular thrombi in patients with an acute anterior myocardial infarction to study the appearance and disappearance of left ventricular thrombi after an anterior myocardial infarction to study the long-term trend in the incidence and event rate of ischemic stroke after a myocardial infarction to study the time relationship between myocardial infarction and ischemic stroke to identify risk factors for ischemic stroke related to a myocardial infarction to study the consequences of a recent myocardial infarction in terms of clinical stroke characteristics to study the risk of a recurrent stroke and the mortality in stroke patients with a recent myocardial infarction
6. Patients

Papers I and III: Ninety-nine patients admitted to the coronary care unit with an evolving anterior myocardial infarction. Patients admitted within 6 hours of the onset of chest pain or with clinical signs of ongoing myocardial ischemia were given streptokinase and aspirin.

Paper II: Seventy-seven patients admitted to the coronary care unit who received streptokinase because of an anterior myocardial infarction.

Paper IV: One-hundred-and-twenty-four case subjects with a stroke within 28 days of an acute myocardial infarction. One-hundred-and-twenty-four control subjects with a myocardial infarction but without a stroke were matched for age, sex and year when the myocardial infarction occurred.

Paper V: One-hundred-and-three case subjects with a first-ever ischemic stroke within 28 days of an acute myocardial infarction. Two controls per case (n=206) with a stroke but without a recent myocardial infarction were matched for age, sex and year when the stroke occurred.
7. Methods

7.1 Papers I, II and III

7.1.1 Diagnostic studies
Anterior myocardial infarction (Papers I,II,III)
A diagnosis of an anterior myocardial infarction was based on typical chest pain resistant to nitroglycerine, a diagnostic elevation of serum creatine kinase and electrocardiographic findings: either the development of pathological Q-waves in two or more precordial leads or ST-segment elevation of $\geq 0.15$ mV in two or more of leads V1-V3 or of $\geq 0.1$ mV in two or more of leads V4-V6.

Cardiac enzyme analysis (Papers I,II,III)
Creatine kinase (CK) and creatine kinase-MB (CKMB) were measured on admission and at fixed hours four times daily. The time to peak CK from the start of therapy was noted. Thermostable lactate dehydrogenase (LD1) was measured on admission and thereafter daily until the maximum level could be identified.

Two-dimensional echocardiography (Papers I,II,III)
Two-dimensional echocardiographic examinations were performed within three days of admission (Papers I,II,III), before discharge (Papers I,II,III) and after one month (Papers II,III), three months (Paper III) and one year (Paper III) of follow-up. An Acuson XP-10 (Acuson Corp., CA, USA) or a Vingmed CFM 750 (Vingmed Sound A/S, Norway) equipped with 2.5-5.0 MHz transducers was used. The examinations were recorded on a Panasonic AG 7330 video tape-recorder and reviewed by two investigators who were unaware of treatment and previous findings.

Left ventricular thrombus (Papers I,II,III)
A left ventricular thrombus was defined as an echodense mass adjacent to an abnormally contracting myocardial segment. It should be distinguished from the underlying myocardium, have a clear thrombus-blood interface and be seen in at least two different projections (20).
Segmental wall motion (Papers I,II,III)
A 16-segment model was used to score the severity of segmental wall motion abnormalities according to the American Society of Echocardiography (219). The scoring scale ranged from 1 to 5. A normally contracting or hyperkinetic segment was assigned a score of 1, hypokinesis 2, akinesis 3, dyskinesis 4 and aneurysmal segments (diastolic deformation) 5. The sum of all scores was calculated for each patient and was used in the statistical analysis.

Doppler measurements (Paper I)
Left ventricular systolic function was investigated by pulsed doppler registrations from the left ventricular outflow tract. The velocity time integral (VTI), maximum velocity (VMAX), mean velocity (VMEAN) and acceleration (dV/dT) were measured.

7.1.2 Treatment (Papers I,II,III)
Thrombolytic treatment consisted of an intravenous infusion of 1.5 million units of streptokinase over a period of one hour. Heparin was not used in any patient. All patients without contraindications were given 160 mg of aspirin daily. Peroral anticoagulants were not routinely used but could be administered at the discretion of the attending physician.

7.2 Papers IV and V
Case-finding (Papers IV and V)
The two northernmost counties of Sweden constitute one of the centres of the World Health Organization (WHO) MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) Project. All stroke events occurring in the age range of 25 to 74 years have been prospectively recorded since 1985 and a particular code has been given to patients with a myocardial infarction within 28 days prior to the stroke. The area has a population of approximately 310000 inhabitants who are between 25 and 74 years of age. Routine case-finding procedures identify 96% of all stroke events (220).

Definition of stroke (Papers IV and V)
The WHO definition of stroke was used: rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than a vascular origin (97).
Definition of myocardial infarction (Papers IV and V)
A diagnosis of myocardial infarction was based on either autopsy findings or typical chest pain, ECG findings and a diagnostic elevation of cardiac enzymes. Two of three of the clinical criteria were required. An anterior myocardial infarction was defined as either the development of pathological Q-waves in two or more precordial leads or an ST-segment elevation of $\geq 0.15$ mV in two or more of leads V1-V3 or of $\geq 0.1$ mV in two or more of leads V4-V6.

Definition of ST-segment elevation (Paper IV)
An ST-segment elevation of $\geq 0.15$ mV in two or more of leads V1-V3 or of $\geq 0.1$ mV in two or more of leads V4-V6 or the extremity leads was evaluated as predictor of stroke.

Incidence and event rate (Paper IV)
Incidence and event rate were used to describe the occurrence of stroke within one month of a myocardial infarction. Event rate was defined as the rate of stroke in a group of patients with a myocardial infarction. The yearly number of patients aged $< 75$ years with a myocardial infarction was obtained from hospital statistics and used to calculate the myocardial infarction related stroke event rate. Incidence was defined as the number of myocardial infarction related strokes per 100000 25- to 74-year-old inhabitants and year.

Daily incidence and daily event rate (Paper V)
Daily incidence and daily event rate were used to describe the daily occurrence of stroke in the MONICA population and the daily stroke rate within 28 days of a myocardial infarction respectively. Daily incidence was defined as the average number of first-ever strokes each day per 10000 25- to 74-year-old inhabitants during the observation period. Age adjustments were made with the myocardial infarction population as a standard population. The daily event rate was defined as the number of strokes each day per 10000 myocardial infarction patients of $< 75$ years of age during the first 28 days following an infarction.

Clinical subclasses of cerebral infarction (Paper V)
A clinical subclassification of the cerebral infarctions in case and control subjects was made according to Bamford et al. (221) using data from the MONICA registry and medical records. Four subclasses were used: total anterior circulation infarcts, partial anterior circulation infarcts, lacunar infarcts and posterior circulation infarcts. The subclassification was made
independently by two investigators and disagreements were resolved by consensus in nine of 309 cases.

Clinical characteristics of stroke patients (Paper V)
The onset characteristics of stroke, course of neurological symptoms during the hospital stay (regression, no change, progression) and impairment of consciousness were recorded. The patients' self-care performance before the stroke event and at discharge was recorded as independent, partly dependent or fully dependent (or dead) (222).

7.3 Statistical analysis

Data were analysed using the STATISTICA 4.0 software modules (StatSoft Inc., OK, USA) (Papers I-V). Group data were expressed as the mean +/- standard deviation (SD) for continuous variables and as rates for variables on a nominal scale. Differences between two means were assessed using Student's t-test for unpaired data or the Mann-Whitney U test when appropriate. Differences between proportions were analysed using the χ²-test or, for small sample sizes, using Fisher's exact test. In all the statistical tests, the null hypothesis was rejected at the 5% level (p<0.05).

Linear regression was used to study the relationship between two variables (Paper IV).

Multiple logistic regression was used to study the relationship between several explanatory variables and a binary dependent variable (Papers I, III). A conditional analysis was performed when the investigation had a case-control design (Paper IV).

The probability of event-free survival during a given period of time was calculated by Kaplan-Meier survival curves and compared between groups using the log-rank test (Papers III-V). The hazard ratio was calculated as a measure of relative survival (Paper III). The Cox proportional hazards model was used to identify important prognostic variables (Papers IV-V). Odds ratios with corresponding 95% confidence intervals for a matched case-control study were calculated (Paper IV).

An equation was fitted to the event-rate data by exponential regression (Paper V).
7.4 Ethical aspects

The echocardiographic studies and the northern Sweden MONICA study have been approved by the Research Ethics Committee at Umeå University. The data-processing procedures in the MONICA study have been approved by the National Swedish Computer Data Inspection Board.
8. Results and discussion

8.1 Incidence of left ventricular thrombi after thrombolytic treatment (Paper I)

Results
The rate of a left ventricular thrombus in the thrombolysis and non-thrombolysis groups was 22% (n=16) vs 38% (n=9) (p=0.11) at three days after admission and 31% (n=23) vs 29% (n=7) (ns) before discharge respectively. The groups were well-balanced in terms of the different clinical characteristics and no differences in segmental myocardial function or in the different doppler measurements of left ventricular function were observed.

A relationship was found between the presence of a thrombus at discharge and a high dose of per-oral diuretics, use of parenteral diuretics, previous myocardial infarction, enzyme levels, segmental myocardial function and doppler measurements of myocardial function. Multiple logistic regression analysis indicated that segmental myocardial dysfunction was the most important predictor of thrombus. An increase of 1 SD (5.6) in segmental score carried a twofold increase in the risk of thrombus (odds ratio 1.8, 95% confidence interval 1.7-2.0).

No embolic events were observed during the hospital stay.

Discussion
Streptokinase in standard doses does not appear to prevent the development of a left ventricular thrombus during the acute phase of an anterior myocardial infarction.

A reduced incidence of left ventricular thrombi after streptokinase in patients with anterior myocardial infarction has been reported in four previous studies (54-56, 59). All these patients were, however, treated with high-dose intravenous heparin after streptokinase. Furthermore, patients in the untreated groups had a higher rate of low ejection fractions or major left ventricular wall motion abnormalities. Heparin reduces the incidence of left ventricular thrombi according to two large trials of patients with an acute anterior myocardial infarction (61, 84). The lower incidence of left ventricular thrombi after streptokinase reported in these studies may therefore be explained both by heparin administration and by preservation of myocardial function.
In two previous studies, subsets of patients were given streptokinase without adjunctive heparin. A thrombus was found in 26% of the patients (9/35 and 14/53 respectively) before discharge (53, 81). These findings are in good agreement with the present study (30%).

Patients treated with streptokinase tended to have fewer thrombi compared with non-treated patients at the first echocardiographic examination (22% vs 38%, p=0.1). This may be a result of the initial thrombolytic state induced by the treatment.

Several authors have investigated the rate of left ventricular thrombi using two-dimensional echocardiography in patients with an anterior myocardial infarction who were not treated with thrombolytics (38, 40, 43, 44, 46). The prevalence reported in these studies ranged between 31 and 46%, in good agreement with the present observations.

In a multivariate analysis, left ventricular segmental function was found to be the most important predictor of a left ventricular thrombus, a finding in agreement with one previous report (81).

No clinically evident embolic event occurred during the hospital stay. A low rate of embolic events has also been reported in other studies of patients with an anterior myocardial infarction who were treated with thrombolysis. Including the present study, only two embolic events were observed in 603 patients with 145 left ventricular thrombi who were given thrombolysis (53-57, 79-81). Most of these patients were also treated with aspirin or heparin or both.

8.2 Appearance and disappearance of ventricular thrombi after an anterior myocardial infarction (Papers II-III)

Results
The formation and resolution of left ventricular thrombi during the follow-up period in consecutive patients with an anterior myocardial infarction and in the subgroup receiving streptokinase is shown in Figures 1-2 and 3-4 respectively.

The majority of the thrombi diagnosed during the hospital stay had resolved at follow-up one month later (81%, 22/27). The resolution of thrombi was common in warfarin-treated patients (91%, 10/11), as well as in untreated patients (75%, 12/16). Similar results were obtained in the subgroup of patients receiving thrombolytics, Figure 3.

A new thrombus was found in some patients at every interval of the follow-up examination, including 12 months after discharge, Figure 2. A large proportion of the thrombi appeared between the first and second examination,
Figure 1. Resolution and reappearance of left ventricular thrombi in patients with a thrombus at discharge. Echocardiographic examinations during follow-up were performed one, three and twelve months after discharge.
Figure 2. Appearance and resolution of left ventricular thrombi in patients without thrombus at discharge. Echocardiographic examinations during follow-up were performed one, three and twelve months after discharge.
Figure 3. Disappearance and reappearance of left ventricular thrombi in patients with a thrombus at the first echocardiographic examination. The patients were examined within three days of admission, before discharge and at 1 month follow-up. T=thrombus. 0=no thrombus.

Figure 4. Appearance and disappearance of left ventricular thrombi in patients without a thrombus at the first echocardiographic examination. The patients were examined within three days of admission, before discharge and at 1 month follow-up. T=thrombus. 0=no thrombus.
Figure 4. Thirty patients had a thrombus at discharge (Figure 1) and in 12 patients a new thrombus appeared during follow-up (Figure 2).

Discussion
This observational study of unselected, prospectively-followed, consecutive patients with an acute anterior infarction reveals that left ventricular thrombus formation and resolution is very dynamic.

There are few data on the in-hospital resolution of left ventricular thrombi in patients with an acute myocardial infarction. In one study of 92 patients with an anterior myocardial infarction, 43 of whom were treated with streptokinase, two of 20 thrombi resolved in patients surviving the hospital period (47). In another study, echocardiography was performed within 48 hours of admission and before discharge in patients treated with streptokinase (53). Ten of 19 thrombi developed and three of 12 thrombi resolved between the examinations. In the present study, a similar proportion of thrombi developed between the first and second examinations (18/35, Figure 4), but resolution of thrombi was more common (11/16, Figure 3).

During short-term echocardiographic follow-up after an anterior myocardial infarction, disappearance of left ventricular thrombi has been reported to occur in a minority of patients. In one study, two of 12 thrombi disappeared during four months of follow-up with anticoagulant treatment (43). In another study, no anticoagulants were used and two of 15 thrombi had resolved 26 days after discharge (44).

When streptokinase was used in approximately half the patients (47%), a thrombus was found in 20 of 92 patients at discharge (47). After 12 weeks of follow-up, with anticoagulant treatment in 15 of the 20 patients, 10 thrombi persisted. Differences in patient recruitment, study design, the treatment and duration of follow-up make it difficult to compare the present results with those of previous reports. In our study, however, the disappearance of thrombi was far more common during the short-term follow-up of patients treated with streptokinase (17/20, 85%, Figures 3 and 4).

In the entire study group, resolution of thrombi formed during the hospital stay was seen in 84% (21/25) after three months (Figure 1). The proportion of thrombi reported to have resolved during long-term follow-up in most previous studies was smaller, ranging between 20% and 58% (44, 46, 49). Oral anticoagulants were routinely used in one study and resolution of thrombi was reported in 33% (4/14) after 12 months of follow-up (43). The treatment of left ventricular thrombi with oral anticoagulants has been
examined in a controlled trial and resolution of thrombi occurred in 59% and 88% of the patients after three and 12 months respectively (90). The high proportion of thrombi which resolved during follow-up in the present study may be associated with new treatment routines after a myocardial infarction. Aspirin reduces thrombo-embolic complications in patients with atrial fibrillation (223) and may modify platelet deposition in some patients with left ventricular thrombi (92). The use of thrombolytics and aspirin may hypothetically influence the thrombus structure and make it more susceptible to endogenous thrombolysis.

8.3 Ischemic stroke after an acute myocardial infarction (Paper IV)

Results
One-hundred and twenty-four cases with a stroke within 28 days of an acute myocardial infarction were identified from 1 January 1985 to 31 December 1994. During the 10-year period, 11620 patients aged < 75 years had a myocardial infarction, giving an overall event rate of ischemic myocardial infarction related stroke of 1.07%. The annual stroke event rate and the incidence of myocardial infarction related ischemic stroke decreased during the study period (p<0.05 and p<0.01 respectively), Figures 5 and 6.

![Graph](image)

Figure 5. Annual event rate of ischemic stroke following acute myocardial infarction between 1 January 1985 to 31 December 1994, \( r^2 = 0.67 \), p<0.05.
Figure 6. Annual number of ischemic strokes following acute myocardial infarction per 100000 inhabitants 25-74 years old between 1 January 1985 to 31 December 1994, $r^2=0.76$, $p<0.01$.

Figure 7 shows the time relationship between the index myocardial infarction and the onset of stroke. Fifty-one per cent of the strokes occurred within five days after the debut of myocardial infarction symptoms.

Figure 7. Cumulative myocardial infarction (MI) related strokes within 28 days.
Autopsy or echocardiography was performed in 37/124 (30%) of patients with a stroke and in 35/124 (28%) of those without. A left ventricular thrombus was found in 7/37 (18%) vs 2/35 (6%), p=0.09.

Different risk factors for myocardial infarction related stroke, calculated as matched odds ratios, are shown in Table 6.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.7</td>
<td>0.96 - 3.17</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2.4</td>
<td>0.99 - 6.14</td>
</tr>
<tr>
<td>Chronic atrial fibrillation</td>
<td>3.0</td>
<td>1.13 - 9.20</td>
</tr>
<tr>
<td>Onset of atrial fibrillation</td>
<td>3.5</td>
<td>1.38 - 10.11</td>
</tr>
<tr>
<td>ST-segment elevation</td>
<td>2.4</td>
<td>1.38 - 4.56</td>
</tr>
<tr>
<td>Anterior location of myocardial infarction</td>
<td>1.5</td>
<td>0.92 - 2.57</td>
</tr>
</tbody>
</table>

In a conditional multiple logistic regression model (p<0.001), a previous stroke (odds ratio (OR) 2.8, 95% confidence interval (CI) 1.1-7.6), chronic atrial fibrillation (OR 3.8, CI 1.3-11.0), new onset atrial fibrillation (OR 4.6, CI 1.6-12.8) and ST-segment elevation (OR 3.4, CI 1.6-7.4) were independent predictors of stroke, while hypertension, anterior location of the myocardial infarction, previous myocardial infarction and signs of heart failure were not. The myocardial infarction related stroke event rate increased with age (p<0.05), Figure 8. No stroke occurred before the age of 40 years. A marked increase in stroke event rate was observed in patients aged 65 years and older.

Discussion

Stroke following an acute myocardial infarction is an uncommon yet serious clinical problem. A possible decrease in the event rate of stroke following myocardial infarction has been suggested but this has been difficult to substantiate because of divergences in patient inclusion, the exclusion of high-risk patients, deviating diagnostic criteria and follow-up times in different studies (157). The present study was population-based, it included a large number of unselected patients and covered a time period of ten years. The
results support a declining trend in the incidence and event rate of myocardial infarction related ischemic stroke. No declining trend in the overall stroke incidence has been observed during the same period of time in the present population (222).

The lower event rate during the last years of the study period, approximately 0.8%, may have several explanations. The general care of patients with an acute myocardial infarction has gradually changed, with early mobilization and the routine use of thrombolytics and aspirin. Aspirin has produced an impressive reduction (42%) in post myocardial infarction stroke in a large randomized study (145).

After adjustments for other clinical variables, atrial fibrillation (chronic or new onset), a previous stroke and ST-segment elevation were identified as independent predictors of stroke in the present study. Older age was also associated with a higher event rate of stroke (Fig 8). These results agree favourably with the findings of Behar et al. (139) and indicate that myocardial infarct size and pre-existing atherosclerosis are more important for the risk of stroke than the appearance of a left ventricular thrombus.

Possible action to avoid a stroke after myocardial infarction thus includes the preservation of myocardium and ventricular function, as well as the prevention of atrial fibrillation, if possible. Moreover, aspirin has shown
an impressive prophylactic effect (145). Alternatively, anticoagulants may be useful, but this treatment is difficult to control and is associated with a significant risk of bleeding (224).

8.4 Impact of a recent myocardial infarction on clinical stroke characteristics (Paper V)

Results

One-hundred-and-three cases with a first-ever stroke within 28 days of an acute myocardial infarction were identified from 1 January 1985 to 31 December 1994. These myocardial infarction-related strokes constituted 1.8% of all first-ever strokes.

A comparison of neurological features in cases and controls is shown in Table 7. The sudden onset of neurological symptoms, impairment of consciousness and progress of neurological deficits were more common in cases, while the onset of stroke during sleep was considerably more common in controls. There were significant differences in clinical subclassification and self-care performance between cases and controls (Table 8). A large proportion of the cases (51.5%) had extensive neurological deficits corresponding to total anterior circulation infarct, while only a few (4.9%) had infarctions of the lacunar infarct subtype. Accordingly, the cases had a poorer self-care performance at discharge.

Figure 9 shows the rate of first-ever ischemic stroke following a myocardial infarction and the corresponding stroke occurrence in the MONICA population after age adjustments. During the month following a myocardial infarction, the daily rate of stroke declined rapidly from approximately nine to one stroke per 10000 myocardial infarction patients, compared with an average age-adjusted stroke rate of 0.14 per 10000 in the population.

Figure 10 shows recurrent strokes over 12 months after a first-ever cerebral infarction in cases and controls. Although there was a clear tendency towards a higher recurrence rate among myocardial infarction patients during the first two months, there was no statistically-significant difference between the two groups over a period of one year (p=0.29). Patients suffering a stroke after a myocardial infarction had a 70% cumulative survival rate at 28 days and a 57% cumulative survival rate at one year. The corresponding figures for patients without a myocardial infarction were 94% and 88%.
Table 7. Stroke characteristics in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=103)</th>
<th>Controls (n=206)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden onset of symptoms</td>
<td>76.7%</td>
<td>54.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset during sleep</td>
<td>6.8%</td>
<td>21.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>35.0%</td>
<td>18.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Partial regression of symptoms</td>
<td>55.3%</td>
<td>71.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>19.4%</td>
<td>8.7%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 8. Clinical subclassification (221), self-care performance and death in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=103)</th>
<th>Controls (n=206)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total anterior circulation infarction</td>
<td>51.5%</td>
<td>37.9%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Partial anterior circulation infarction</td>
<td>28.2%</td>
<td>26.7%</td>
<td>ns</td>
</tr>
<tr>
<td>Lacunar circulation infarction</td>
<td>4.8%</td>
<td>27.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior circulation infarction</td>
<td>15.5%</td>
<td>8.2%</td>
<td>=0.051</td>
</tr>
<tr>
<td>SCP before stroke event, independent</td>
<td>96.1%</td>
<td>94.7%</td>
<td>ns</td>
</tr>
<tr>
<td>SCP at discharge, independent</td>
<td>35.9%</td>
<td>55.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>partly dependent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fully dependent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead during hospital stay</td>
<td>30.1%</td>
<td>6.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SCP=Self-care performance, ns=not significant
Figure 9. The daily number of first-ever strokes per 10,000 patients with myocardial infarction during the first 4 weeks following the infarction ($y=1.08+\exp(2.1-0.15x)$, $r^2=0.74$). For comparison, the average age-adjusted daily number of first-ever strokes per 10,000 subjects in the northern Sweden MONICA population is shown (0.14 events per day).
Figure 10. Cumulative percentage without a recurrent stroke during one year of follow-up in cases and controls (p=0.29, log-rank test).
Discussion
The present study confirms the detrimental effect of a stroke following a myocardial infarction. The neurological deficit is more extensive, the clinical course more adverse and the mortality rate higher compared with a stroke in patients without a recent myocardial infarction.

In spite of the differences in clinical characteristics, no single clinical finding or combination of findings is specific enough to differentiate between a cardiogenic and non-cardiogenic stroke in the individual patient.

Figure 9 shows that the risk of stroke declines exponentially and the equation fitted to the present data explained 74% of the variance. In the SAVE study, the rate of stroke during the long-term follow-up of patients with ventricular dysfunction after myocardial infarction was 1.5% per year, corresponding to 0.41 stroke events per day per 10000 subjects (162). Although the risk of a stroke following a myocardial infarction is much higher than the risk of a stroke in the population in general, the absolute numbers are still low. During a 10-year period, a first-ever ischemic stroke was diagnosed in 103 of 11620 patients (0.9%) during the first 28 days following a myocardial infarction.

The risk of a recurrent stroke was similar in case and control subjects during one year of follow-up (13.6% vs 12.1%, p=0.29), Fig. 10. The risk of a recurrent thrombo-embolic event following a myocardial infarction has previously been estimated at between 30% to 50% (194). These data are based on heterogeneous and small-sized studies, often autopsy series (2, 195), making the results unreliable and probably not applicable to patients receiving modern treatment, including aspirin and thrombolytics. The rate of recurrent stroke in the present control group agrees favourably with other epidemiological studies (112, 221).
9. Conclusions

Thrombolytic treatment within 6 hours from onset of chest pain in consecutive patients with anterior myocardial infarction does not reduce the occurrence of left ventricular thrombi. The risk of thrombus formation is related to the size of the myocardial injury.

The development and resolution of left ventricular thrombi after an anterior myocardial infarction is a highly dynamic process. Most thrombi diagnosed during the hospital stay resolve within one month irrespective of thrombolytic treatment. Formation of new thrombi continues during the first year after discharge.

There is a long-term trend towards a lower incidence and event rate of ischemic stroke after a myocardial infarction.

The risk of ischemic stroke is highest within the first few days following a myocardial infarction. Of all strokes occurring within 28 days, approximately half occur during the first five days.

Atrial fibrillation (chronic or new onset), ST elevation and a history of a previous stroke are independent predictors of ischemic stroke after a myocardial infarction.

When stroke-patients with and without a recent myocardial infarction are compared, those with a preceding myocardial infarction more often have a sudden onset of neurological symptoms, an impairment of consciousness, a progress of neurological deficits and a stroke of the total anterior circulation infarct subclass. However, the clinical characteristics are not specific enough to differentiate between a cardiogenic and non-cardiogenic stroke in an individual patient.

The risk of a recurrent stroke over 12 months is not influenced by a recent myocardial infarction, but myocardial infarction patients have a markedly higher mortality.
10. Acknowledgements

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11. References


