Clinical practice

Individual risk assessment for intracranial haemorrhage during thrombolytic therapy

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Summary

Thrombolytic therapy improves outcome in patients with myocardial infarction but is associated with an increased risk of intracranial haemorrhage. For some patients, this risk may outweigh the potential benefits of thrombolytic treatment. Using data from other studies, we developed a model for the assessment of an individual's risk of intracranial haemorrhage during thrombolysis.

Data were available from 150 patients with documented intracranial haemorrhage and 294 matched controls. 49 patients with intracranial haemorrhage and 122 controls had been treated with streptokinase, whereas 88 cases and 148 controls had received alteplase. By multivariate analysis, four factors were identified as independent predictors of intracranial haemorrhage; age over 65 years (odds ratio 2·2 [95% CI 1·4–3·5]), body weight below 70 kg (2·1 [1·3–3·2]), hypertension on hospital admission (2·0 [1·2–3·2]), and administration of alteplase (1·6 [1·0–2·5]).

If the overall incidence of intracranial haemorrhage is assumed to be 0·75%, patients without risk factors who receive streptokinase have a 0·26% probability of intracranial haemorrhage. The risk is 0·96%, 1·32%, and 2·17% in patients with one, two, or three risk factors, respectively. We present a model for individual risk assessment that can be used easily in clinical practice.

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Introduction

Thrombolytic therapy improves immediate and long-term survival[1-4] and quality of life[5] in patients with evolving myocardial infarction; however, it also carries a small but significant risk of severe bleeding complications, including intracranial haemorrhage. A physician must decide for each individual patient whether the potential benefits of thrombolytic therapy[6] outweigh the risk. Previous studies have shown that age, hypertension, a high dose of thrombolytic for a given body weight, being female, previous central nervous system disease, and use of oral anticoagulants are associated with increased bleeding risk after thrombolytic therapy.[7-12] However, the numbers of patients in each of these studies are small and risk assessment in individual patients remains uncertain.

In this report, data from several studies[7-11,13-23] were combined to collect a larger database for statistical evaluation, so that we could develop a risk profile for intracranial haemorrhage that can be applied to individual patients to assess the appropriateness of thrombolytic therapy.

Patients and methods

Individual patient data were collected from five sources: a registry of thrombolytic therapy in the Netherlands in 1988–90,[10] combined with data from two studies by the European Cooperative Study Group,[10,16,17] and for participants in the GISSI-II and International Study Group trials,[11,13,14] the TIMI II trials,[7,8,18,19] studies by the TAMI group,[9,20-23] and the ISAM study.[15]

In the Netherlands 2469 patients receiving thrombolytic therapy in 61 hospitals were registered prospectively during 18 months in 1988–90. The registry sought to collect all patients who received thrombolytic therapy for evolving myocardial infarction.[10] No specific entry or exclusion criteria and no formal criteria for administration of thrombolytic therapy were applied. However, treatment of patients aged 75 years and older and treatment starting later than 6 h after symptom onset was unusual at that time. Most patients received streptokinase, usually with aspirin and intravenous heparin. 24 patients were identified who developed intracranial haemorrhage within 48 h of the start of thrombolytic therapy, and complete data were available for 22 of them. We also included 2 patients who had intracranial haemorrhages at the Thoraxcenter, Rotterdam, and 7 patients of 722 treated with alteplase in two studies by the European Cooperative Study Group.[16,17] Full details have been presented elsewhere.[10]

In the GISSI-2 and International Studies, complete data were available for 20 768 patients who were randomly assigned either 1·5 MU streptokinase or 100 mg alteplase. That study had no age limit but patients with a history of cerebrovascular events in the preceding 6 months were not eligible.[13] All patients received aspirin and half received subcutaneous heparin, starting 12 h after initiation of thrombolytic therapy. Strokes were reported in 236 patients (1·14%), of which 100 were of embolic origin, 74 were haemorrhagic, and 62 could not be classified.[11]

	NL and ECSG		GISSI-2		TIMI		TAMI		ISAM		Combined trials	
	ICH	C	ICH	C	ICH	C	ICH	C	ICH	C	ICH	C
n	31	62	74	142	27	54	14	28	4	8	150	294
No (%) male	27 (57)	48 (77)	47 (63)	112 (79)	16 (60)	43 (80)	7 (50)	23 (87)	2 (50)	66 (75)	98 (65)	52 (79)
Mean (SD) age in yr	65 (8)	58 (10)	66 (11)	60 (12)	63 (8)	56 (9)	65 (7)	54 (12)	63 (8)	58 (12)	65 (8)	58 (11)
Infarct location*												
Anterior	14	19	25	59	15	30	5	11	3	3	62	122
Inferior	16	38	12	26	12	24	9	17	1	5	50	110
Inferoposterior	10	24	..	..	..	..	..	..	..	..	10	24
Lateral	5	11	..	..	..	..	..	..	..	..	5	11
Unknown	1	3	37	57	..	..	..	..	..	..	38	60
Thrombolytic drug												
Streptokinase	15	35	30	79	..	..	..	..	4	8	49	122
Alteplase	10	20	44	63	27	54	7	11	..	..	88	148
(pro-)Urokinase	3	6	..	..	..	..	4	6	..	..	7	12
Alteplase + urokinase	..	..	..	..	..	..	3	11	..	..	3	11
Anistreplase	3	1	..	..	..	..	..	..	..	..	3	1

NL = Netherlands Registry; ECSG = European Cooperative Study Group;[10] GISSI-2 = Gruppo Italiano per lo Studio della Sopravvivenza nell 'Infarto Miocardico B and the International Study Group;[11,13,14] TIMI = Thrombolysis in Myocardial Infarction, phase II;[9] TAMI = Thrombolysis and Angioplasty in Myocardial Infarction;[9,20–24] ISAM = Intravenous Streptokinase in Acute Myocardial infarction.[15]

*Different criteria were used by the various study groups; in some patients multiple infarct locations were reported simultaneously.

Table 1: **Baseline data for 150 patients with intracerebral haemorrhage (ICH) and 294 matched controls (C)**

In the TIMI phase II pilot study and clinical trial, 908 patients were treated with 150 mg alteplase and 3016 patients with 100 mg alteplase, both in combination with heparin and aspirin.[18,19] Intracranial haemorrhages were observed in 27 patients (23 intracerebral, 4 subdural[18]), of whom 14 had received 150 mg alteplase and 13 had received 100 mg. The TIMI studies enrolled patients up to the age of 75 years. Initially, patients with a history of active cerebrovascular disease during the previous 6 months were not eligible. After revision of the protocol,[7] all patients with a history of stroke were excluded, as well as patients with blood pressures above 180 mm Hg systolic or 110 mm Hg diastolic at presentation. At first, aspirin 80 mg was started on the same day as thrombolytic therapy. The protocol was revised, and in most patients (3297) aspirin was not started until the next day. Heparin was given as a 5000 IU bolus at the start of alteplase infusion, and continued at 1000 IU per h. Subsequently, the dose was adjusted to maintain the activated prothrombin time (APTT) between 1·5 and 2·0 times control. After day 6, intravenous heparin was replaced by subcutaneous heparin and aspirin was increased to 325 mg daily.[8,15,16]

The TAMI studies[9,20–23] enrolled 1619 patients up to 75 years of age, excluding those with recent (6 months) trauma, recent major surgery or active internal bleeding, known structural brain disease including tumour or arteriovenous malformation, stroke within the previous 6 months, and uncontrolled hypertension (diastolic pressure > 120 mm Hg by several measurements). Strokes were reported in 31 patients, 14 of whom had intracranial haemorrhage (0·9% of all patients). Thrombolytic therapy consisted of alteplase, in doses of 64–150 mg, plus urokinase (1·5–2·0 MU) or 3 MU urokinase alone in some of the patients. Heparin infusion was started during diagnostic and interventional cardiac catheterisaton, and maintained continuously for a minimum of 24 h, adjusted to maintain APTT between 1·5 and 2·0 times baseline. Aspirin was started during thrombolytic therapy and continued at 325 mg daily together with dipyridamole 75 mg 3 times daily.

The ISAM study[15] enrolled 1741 patients. The age limit was 75 years. Reasons for exclusion were known haemorrhagic diathesis, use of anticoagulants, severe treatment-resistant hypertension (systolic ⩾200 mg Hg, diastolic ⩾120 mm Hg), trauma, stroke, acute headache, visual disorders of unknown origin, trauma, or increased gastrointestinal bleeding risk. Intracranial haemorrhage was reported in 4 patients. All patients received streptokinase 1·5 MU in 1 h, as well as methylprednisolone, intravenous aspirin 500 mg and heparin, followed by phenprocoumon for at least 3 weeks.

For each patient in these studies with intracranial haemorrhage, 2 controls were selected from the same population. The controls were patients treated in the same hospital, immediately before and after each patient with intracranial haemorrhage. For all cases and controls we recorded sex, age, body weight, the presence of insulin-dependent diabetes mellitus, vascular disease (history of intermittent claudication or vascular bruits before admission), hypertension before admission (patients receiving at least one antihypertensive drug), the use of anticoagulants before admission, smoking status, hypertension on admission (systolic ⩾165 mm Hg, diastolic ⩾95 mm Hg, or both). We also recorded whether the patient received heparin, antiplatelet drugs, and anticoagulants during the hospital stay.

Differences in clinical characteristics between patients with intracranial haemorrhage and controls were expressed as crude or univariate odds ratios with 95% CI. Multivariate logistic regression analysis was done with the BMDP statistical package. All variables and interaction terms were entered into the model.

	All patients			Alteplase-treated patients			Streptokinase-treated patients		
	ICH+	ICH−	Odds ratio (95% CI)	ICH+	ICH−	Odds ratio (95% CI)	ICH+	ICH−	Odds ratio (95% CI)
Age > 65 yr	82/173	68/270	2·7 (1·8–4·0)	52/93	42/166	3·7 (2·2–6·4)	25/75	25/96	1·4 (0·7–2·8)
Weight < 70 kg	76/171	74/272	2·1 (1·4–3·2)	51/99	43/160	2·9 (1·7–4·9)	25/71	25/100	1·6 (0·8–3·2)
Female	52/113	98/330	2·0 (1·3–3·1)	39/67	55/192	3·5 (1·9–6·2)	12/44	38/127	0·8 (0·4–1·9)
Previous hypertension	63/158	84/270	1·5 (1·0–2·2)	42/99	51/151	1·4 (0·9–2·4)	19/57	29/108	1·4 (0·7–2·7)
Hypertension in hospital	49/108	100/334	1·9 (1·2–3·0)	27/56	66/202	1·9 (1·1–3·5)	19/48	31/123	1·9 (1·0–3·9)
Vascular disease	6/12	65/202	2·1 (0·6–6·8)	4/8	45/142	2·2 (0·5–9·0)	1/3	15/48	1·1 (0·1–13·1)
Diabetes	19/52	129/386	1·1 (0·6–2·1)	11/31	82/226	1·0 (0·4–2·1)	7/20	42/148	1·4 (0·5–3·6)
Smoking	58/208	88/218	0·6 (0·4–0·9)	35/120	56/126	0·5 (0·3–0·9)	20/83	29/84	0·6 (0·3–1·2)
History of coumadin treatment	5/8	71/218	3·5 (0·8–15·0)	..	50/152	..	3/6	17/55	2·2 (0·4–12·2)
Coumadin in hospital	6/31	54/151	0·4 (0·2–1·1)	3/13	33/97	0·6 (0·2–2·3)	2/17	16/42	0·2 (0·0–1·1)
Aspirin in hospital	46/171	41/78	0·3 (0·2–0·6)	29/118	26/48	0·3 (0·1–0·6)	15/47	11/23	0·5 (0·2–1·4)
Heparin in hospital	70/203	39/118	1·1 (0·7–1·7)	50/144	18/49	0·9 (0·5–1·8)	16/49	19/66	1·2 (0·5–2·7)

ICH+ = the number of intracranial haemorrhages among patients with a characteristic and ICH− = the number in patients without that characteristic.

Table 2: **Distribution of risk factors for intracranial haemorrhage, incidence of intracranial haemorrhage, and unadjusted odds ratios**

	ICH+	ICH−	Adjusted odds ratio (95% CI)
Age > 65 yr	77/168	66/261	2·2 (1·4–3·5)
Weight < 70 kg	76/170	67/259	2·1 (1·3–3·2)
Hypertension on admission	46/100	97/325	2·0 (1·2–3·2)
Alteplase	93/258	50/171	1·6 (1·0–2·5)

Table 3: **Incidence of intracranial haemorrhage and adjusted odds ratios in 429 patients with complete data**

With step-up and step-down procedures we selected the variables that contributed independently to the risk of intracranial haemorrhage ($p < 0.05$). The initial analysis included all patients with complete data sets to detect independent risk factors. Subsequently, the analysis was done with the larger number of patients for whom data on the risk factors retained in the initial analysis were complete. Data were presented as adjusted odds ratios with corresponding 95% CI. By Bayes' rule, probabilities were calculated for intracranial haemorrhage in four patient groups with no, one, two or three risk factors, respectively.[24]

Results

Data were available for 150 patients with intracranial haemorrhage and 294 matched controls. The other 6 control patients had incomplete data. The series consisted of 145 patients with intracerebral bleeding and 5 with subdural haematoma. Diagnosis of intracranial haemorrhage was confirmed by computed tomography in most patients, and in others by necropsy or clinical findings. The mean age was significantly higher ($p < 0.00001$) in the patients with intracranial haemorrhage than in the controls (table 1). There was also a significant difference between the groups in the proportion of women ($p = 0.002$). Infarct location was classified in different ways by the four study groups. Nevertheless, we found no differences in infarct location between the patient groups. In particular, no excessive bleeding risk was apparent in patients with anterior infarction. The incidence of documented intracranial haemorrhage was 0·9 (0·6–1·3)% in the registry from the Netherlands, 1·0% in the two trials by the European Cooperative Study Group, 0·4% in the GISSI-2 and International Studies (with another 0·3% unclassified strokes), 1·5% in TIMI patients receiving 150 mg alteplase and 0·4% in those receiving 100 mg alteplase, 0·9% in the TAMI studies, and 0·5% in the ISAM study. Our study could not investigate the risks of intracranial haemorrhage with all the thrombolytic regimens included. Nevertheless,

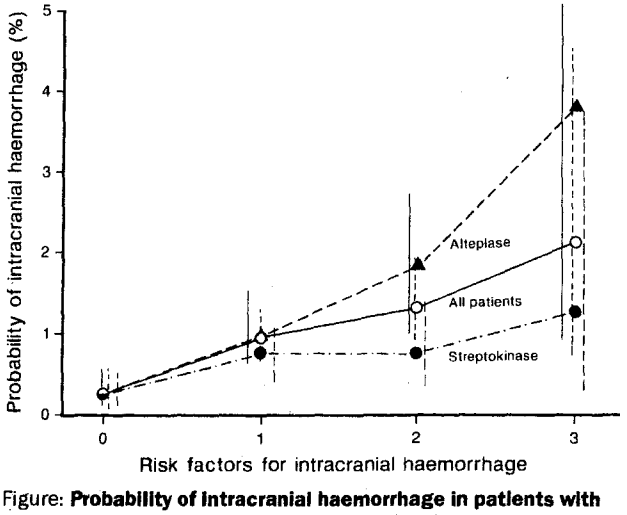

Figure: **Probability of intracranial haemorrhage in patients with 0, 1, or 3 risk factors**
Vertical bars = 95% CI.

Risk factors*	Incidence (%)†	Likelihood ratio‡	Probability of intracranial bleeding (95% CI) in %	
			Incidence = 0·50	Incidence = 0·75
0	53	0·34	0·17 (0·10–0·27)	0·26 (0·15–0·41)
1	31	1·28	0·64 (0·47–0·88)	0·96 (0·70–1·32)
2	15	1·77	0·88 (0·60–1·28)	1·32 (0·92–1·91)
3	1	2·89	1·43 (0·61–3·31)	2·17 (0·92–4·83)

*Risk factors: age ≥ 65 years, body weight < 70 kg, hypertension on admission, and the use of an alteplase regimen. † Derived from studies by European Cooperative Study Group.[16,17] ‡ Probability of finding the risk profile among patients with intracranial bleeding divided by probability of finding the same risk profile among patients without intracranial bleeding. Probability of intracranial bleeding was calculated from overall incidence and likelihood ratio with Bayes' rule.

Table 4: **Probability of intracranial haemorrhage after a thrombolytic regimen as used in these studies**

it was apparent that a greater proportion of patients who had intracranial haemorrhages had received alteplase in various doses, whereas more controls had received streptokinase (table 1).

The distribution of possible risk factors for intracranial haemorrhage is given in table 2. Advanced age, low body weight, female sex, and high blood pressure were associated with an increased risk of intracranial bleeding. Among the five patient series trends were similar, although many were not statistically significant within different series because of small patient numbers. Odds ratios were greater than 2·0 in all series for age and body weight and in 4 of 5 for female sex. Few patients were taking coumadin or had a history of peripheral vascular disease, and no significant association with intracranial bleeding could be detected. Smoking was associated with a reduced intracranial bleeding risk. Furthermore, there was an apparently reduced risk associated with the use of aspirin in hospital, as well as with the use of coumadin in hospital, in the two series for which these data were available.

For most risk indicators the association with intracranial haemorrhage was stronger among alteplase than among streptokinase recipients (table 2). For example, among patients treated with streptokinase, the dose indices (dose/body weight) in patients with intracranial haemorrhage and in controls were, respectively, 28 409 (7012) and 30 600 (6308) IU/kg ($p = 0.40$). The corresponding dose indices for alteplase were 1·61 (0·37) and 1·46 (0·31) mg/kg ($p < 0.01$). After exclusion of TIMI II patients who received 150 mg alteplase, the dose indices were 1·48 (0·24) mg/kg and 1·37 (0·21) mg/kg ($p < 0.01$).

Multivariate logistic regression analysis showed that four factors known at hospital admission were related to risk of intracranial haemorrhage—age over 65 years, weight under 70 kg, hypertension on admission (systolic ≥ 170 mm Hg, diastolic ≥ 95 mm Hg, or both), and drug regimens with alteplase in the doses used. The results of this analysis were similar for patients who had all data available (not shown) as well as for 429 patients (including 143 with intracranial haemorrhage) who had complete data for the variables retained in the multivariate model (table 3). Exclusion of patients with subdural haematoma did not affect the results. The analysis was repeated in various subgroups. In 258 patients who received alteplase the odds ratios for age, low body weight, and hypertension were 3·2 (1·8–5·6), 2·5 (1·4–4·4), and 2·0 (1·0–3·9), respectively. The corresponding odds ratios in 171 patients who received streptokinase were 1·3 (0·7–2·0), 1·6 (0·8–3·1), and 1·9 (0·9–4·0) (figure). Since the administration of 150 mg alteplase has been linked to excessive intracranial bleeding,[7] we repeated this analysis after exclusion of patients who received such therapy. In the remaining 220 alteplase

	Age (yr)			
	<65	66–75	76–85	>85
Other risk factors*				
0	0·3	1·0	1·5	2·3
1	1·0	1·3	2·0	2·9
2	1·3	2·2	3·3	5·0

Based on data in table 4, with following assumptions: overall incidence of intracranial haemorrhage = 0·75%; risk at ate 76–85 is 50% greater than at age 66–75; risk in patient >85 years is again 50% greater than at 75–85. *Hypertension on admisison, low body weight, and use of alteplase.

Table 5: **Assessment of risk of intracranial haemorrhage in different age groups**

recipients the odds ratios were 3·3 (1·8–6·2), 2·5 (1·4–4·7), and 1·6 (0·8–3·4), respectively.

From the data in table 3, we developed a model to predict the risk of intracranial haemorrhage in an individual patient (tables 4 and 5). The odds ratios for the different risk factors were similar. Accordingly, these risk factors were given similar weights in the model and patients were grouped having one, two or three, and four risk factors. Assuming a 0·75% overall intracranial bleeding risk, the individual risk estimate varies from 0·26% for a patient without risk factors who received streptokinase to 5·0% for an elderly hypertensive patient with low body weight treated with alteplase.

Discussion

Haemorrhagic stroke accounts for 10–15% of all strokes in the general population.[25,26] Risk factors for haemorrhagic stroke include advanced age, hypertension, trauma, vascular malformations, and the use of anticoagulants.[25,27] Most trials of anticoagulant drugs have excluded patients thought to be at high risk of intracranial haemorrhage, either by protocol or by prudent physicians when established risk factors were recognised. Nevertheless, thrombolytic therapy seems to be associated with an increased incidence of intracranial haemorrhage, albeit with a concomitant reduction in embolic stroke rates.[1,2] About half of all strokes after myocardial infarction are haemorrhagic when thrombolytic therapy is used.[8,11]

The risk factors for embolic stroke and intracranial bleeding differ. Patients at increased risk of embolic stroke, especially those with large anterior infarctions, should not be denied thrombolytic therapy. In fact, thrombolysis is specifically indicated for such patients, since it gives the greatest survival benefit in patients with larger infarcts.[1-3] Limitation of infarct size and the thrombolytic effect do reduce the risk of left ventricular thrombi. On the other hand, risk factors for haemorrhagic stroke that can be recognised at hospital admission should be taken into account when a decision is made to administer a thrombolytic drug to a given patient.

Various features were found to be associated with the risk of intracranial haemorrhage in the studies included in our analysis. To obtain a larger database, the data were combined in our investigation. By multivariate logistic regression, four factors were independently associated with intracranial bleeding. Advanced age and high blood pressure are patient characteristics readily discernible before the decision on whether to give thrombolytic therapy is made. The associations with body weight and the use of alteplase mean that the choice of thrombolytic regimen must take into account the body size of a patient. Several other characteristics, which are known risk factors for intracranial haemorrhage in population studies, were associated with the disorder in univariate analysis but did not seem to have independent predictive value in multivariate analysis. For example, therapy with coumadin was associated with intracranial haemorrhage in the series from the Netherlands (odds ratio 3·7 [0·8–16·5]) where such therapy is practised in many patients with a previous infarction.[10] Similarly, a history of peripheral vascular disease or diabetes is likely to be associated with intracranial haemorrhage,[22] but these findings were rare and the associations were not powerful enough to appear in the multivariate analysis.

The association between age over 65 years and risk of intracranial haemorrhage was apparent even though some studies excluded patients over 70[16,17] or over 75.[18-23] In larger population surveys of stroke, rates increase with age.[28] In such surveys embolic or thrombotic strokes are most frequent, although few surveys make a distinction between different types of stroke. Accordingly, the data presented in table 5 were calculated with the assumption that risks for intracranial haemorrhage during thrombolytic therapy increase with age in the same way as total stroke risk in the population.

High blood pressure on admission was a stronger predictor of intracranial haemorrhage than a history of hypertension (table 2). This finding suggests that the bleeding risk depends not only on the state of the intracranial vessels, but also, and predominantly, on the actual blood pressure at the time of thrombolytic therapy. This notion is consistent with the observation that, at the time of hospital admission, more patients with intracranial haemorrhage than with other types of stroke showed high blood pressure.[26] Prompt correction of high blood pressure is recommended in all infarct patients, but especially before or during thrombolytic therapy to reduce risk of bleeding.

Low body weight was associated with increased risk of intracranial haemorrhage in patients treated with alteplase. GISSI-2 and the International Study Group did not find an association between body-mass index and haemorrhagic or all strokes in patients receiving thrombolytic therapy.[11] However, body-mass index is a measure of the extent of obesity, not actual weight or total body mass. Reanalysis of GISSI-2 and International Study Group data confirmed the association between intracranial haemorrhage risk and body weight for patients receiving alteplase, whereas no relation was observed in streptokinase recipients (A P Maggioni, M G Franzosi, personal communication). Weight-adjusted dosing for alteplase has been recommended previously, and has been introduced in clinical practice,[21,22] although "front-loaded" alteplase regimens use a fixed dose schedule.[29] Our analysis implies that weight-adjusted dosing should also be considered for streptokinase. Future analysis of data from the GUSTO study may help to resolve this issue.[30]

Previous studies showed that intracranial haemorrhage is more common among patients treated with "standard" doses of alteplase[11] or duteplase[2] than in those given streptokinase. These observations are supported by our analysis (table 3). These figures correspond to the actual drug regimens used in the studies. Alteplase was given in most patients as a fixed dose of 100 mg over 3 h. This dose was selected from studies that showed more rapid coronary reperfusion in comparison with lower doses and with standard streptokinase.[31-33] It is not surprising that a regimen with greater thrombolytic efficacy results in more frequent side-effects, including intracranial haemorrhage. If patients are treated with alteplase, the bleeding risk can be reduced by lowering the dose. Administration of 50 mg

alteplase, for example, gives the same coronary reperfusion rate as 1·5 MU streptokinase.[31,32] However, the survival benefits of that regimen have not been established. Still, an increased risk of intracranial haemorrhage would be acceptable if the survival benefits of such an intensive regimen exceeded those of a more moderate streptokinase regimen. The net clinical benefit should be positive. In ISIS-2,[2] the number of survivors without neurological sequelae was slightly higher (although not significantly so) in duteplase recipients than in streptokinase recipients.[2] On the other hand, in GISSI-2 the net clinical benefit was somewhat greater for streptokinase.[13,14] In the GUSTO trial, the greatest net clinical benefit was found for the accelerated alteplase regimen, despite a greater rate of intracranial haemorrhage in comparison with two streptokinase regimens.[30]

In addition to the thrombolytic agent, most patients receive an inhibitor of platelet aggregation (aspirin) as well as an anticoagulant (heparin, either intravenously or subcutaneously). In our analysis, neither aspirin nor heparin given in hospital was associated with risk of intracranial haemorrhage, probably because the study protocols delayed use of these drugs until several hours after thrombolysis. Obviously, aspirin and heparin would be withheld if signs of intracranial haemorrhage became apparent in the first hours after initiation of thrombolytic therapy.

Risk assessment

The model presented in tables 4 and 5 may help a doctor to estimate the risk of intracranial haemorrhage in a given patient. If the overall risk of intracranial haemorrhage is 0·75%, the risk would be as low as 0·26% in patients without risk factors, who met the entry and exclusion criteria of the studies in this analysis. The probability of intracranial haemorrhage increased with the number of risk factors present. If the overall risk of intracranial haemorrhage is lower (0·50%), the risks would be 0·88% and 1·43% in patients with two or three risk factors, respectively. The risks should be multiplied by 1·6 if the thrombolytic to be used is alteplase (figure).

This assessment of intracranial haemorrhage risk is somewhat crude, and does not account for factors that are likely to increase the risk although present in a smaller subgroup of patients, such as a history of extensive peripheral vascular disease, diabetes, and use of oral anticoagulants. The studies included enrolled patients younger than 75 years, with the exception of GISSI-2 and the International Study Group. Since the risk of intracranial haemorrhage increases with age, the risk in patients aged 75–85 years should be estimated as 1·5 times greater than that in patients of 65–75 years and 50% higher again in patients above 85 years of age[28] (table 5). Furthermore, in these and all other studies of thrombolysis, patients with recognised excessive risk of intracranial haemorrhage were excluded either by protocol, or by the doctors responsible for their treatment. Nevertheless, groups of patients with different risk profiles can be distinguished for individual clinical decision-making with the aid of our model.

Conclusion

In patients with evolving myocardial infarction thrombolytic therapy salvages part of the myocardium at risk and improves survival. However, in a small number of patients thrombolytic therapy causes intracranial haemorrhage, which often results in death or disability. In each patient the doctor should estimate the potential benefits and risks of thrombolytic therapy. Earlier studies addressed the question of which patients will benefit from thrombolysis.[6] This report identifies the factors associated with increased risk of intracranial haemorrhage—advanced age, hypertension upon admission, low body weight, and thrombolysis with current alteplase regimens. Thrombolytic therapy should nevertheless be given to elderly and hypertensive patients if the expected benefits are great—eg, in patients with extensive (anterior) ischaemia who can be treated soon after symptom onset.[1-3,6] A careful evaluation of the applicability thrombolytic therapy is warranted in patients with several risk factors for intracranial haemorrhage.

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Drug profile

Moclobemide

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Background

To understand the development of moclobemide, a selective monoamine oxidase inhibitor (MAOI) for use in depression, we need to consider its origins in antituberculosis drugs. Thus, iproniazid was noted to cause euphoria[1] in tuberculous patients, but this reaction was thought to be a response to their poor physical state. Kline's proposal[1] that these drugs were in fact antidepressant was an important landmark in psychiatry, since the only effective treatment for depression until then was electroconvulsive therapy. Their action in brain led to the agents being described as MAOIs; they came into clinical use in 1959, the same year as the first tricyclic antidepressant (TCA), imipramine.

Iproniazid had to be withdrawn because of an association with acute hepatic necrosis (the mechanism of which is still unclear) and was replaced by isocarboxacid and phenelzine. In the 1960s the toxic effects resulting from absorption of dietary tyramine ("cheese reaction") became apparent; this reaction was the result of inhibition of intestinal MAO, which can provoke a hypertensive crisis. Tranylcypromine (a non-hydrazine MAOI related to amphetamine) was the most troublesome drug in this respect but also the most efficacious. In addition, MAOIs were incompatible with drugs containing indirectly acting sympathomimetic agents and with most forms of alcohol.

Two early trials showed that results with phenelzine were not significantly different from those with placebo in depressed patients, but the experience of many clinicians was far more positive and the trial results may have come about because the maximum dose was too low and the period of treatment too short. Because MAOIs then had to be prescribed with dietary and other restrictions interest shifted away, and their clinical use virtually ceased in most countries. However, some researchers proposed that "atypical" forms of depression responded better to MAOIs than to TCAs. Although the evidence remains uncertain, there is no doubt that individuals vary in their response to antidepressants, and that some with typical endogenous depression who do badly with TCAs may be greatly improved by MAOIs. This response may be related to the fact that MAOIs increase blood concentrations of serotonin, whereas TCAs lower them.[2] Inhibition of MAO decreases the metabolism of noradrenaline and serotonin, leading to increased concentrations of these neurotransmitters. MAOIs have also been shown effective in controlling anxiety disorders, but this action has not been evaluated adequately.

The classic MAOIs were irreversible in that body concentrations of MAO did not return to normal until 2 weeks after the end of treatment because new enzyme had to be synthesised. Consequently, drugs that might cause toxic interactions, including TCAs, could not be introduced

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