

Anticoagulant vs Anti-Platelet Therapy As Prophylactic Against Cerebral Infarction in Transient Ischemic Attacks

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SUMMARY 156 patients with transient ischemic attacks (TIA) or reversible ischemic neurological deficit (RIND) were given prophylactic anticoagulant (AC) treatment against cerebral infarction in a prospective multicenter study from 5 hospitals in southern Sweden. After 2 months of AC treatment, 135 patients remained in the study and were randomized into 2 groups; one continued with AC treatment and one changed to anti-platelet therapy. The patients were followed for 12 months. No significant difference was seen between the 2 groups but 3 completed cerebral infarctions occurred during anti-platelet therapy against one during AC treatment. One cerebral hemorrhage was seen during AC treatment. All completed strokes occurred in men who initially had carotid symptoms. The number of patients with TIA/RIND was somewhat higher in the anti-platelet group whereas myocardial infarctions occurred more often during AC treatment. Compared to the natural history of untreated TIA/RIND both treatments were found to have a prophylactic effect against cerebral infarction.

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ANTICOAGULANT (AC) treatment has been used for nearly 30 years as prophylactic treatment against cerebral infarction in patients who have had transient cerebral attacks (TIA). A decrease in the frequency of cerebral infarctions compared to the natural course in patients with TIA has been reported in several studies (for review see Millikan and McDowell 1978).¹ However, the efficacy of AC treatment has been questioned due to the lack of randomized control groups in the studies favoring anticoagulants.^{2, 3} In addition, there is a risk of bleeding complications which is about 10% even in well-controlled patients.⁴

Recently, prophylaxis against cerebral infarction with anti-platelet therapy has proved useful in patients with TIA^{5, 6} and our purpose has been to study the prophylactic effect of AC treatment compared with that of anti-platelet therapy on patients with TIA and reversible ischemic neurological deficit (RIND). As we have found for several years that AC treatment is valuable as prophylaxis against cerebral infarctions in patients with TIA/RIND,⁴ we gave all the patients AC treatment during the first 2 months, when the risk of cerebral infarction is highest.⁷ Thereafter, the patients were randomized.

Material and Methods

During 9 months in 1977, 156 patients entered the study at 5 hospitals in southern Sweden. All patients were examined by one of us (J.-E.O.) and had either TIA with symptoms disappearing within 24 h or had RIND with slight symptoms persisting more than 24 h

according to the definition given by Meyer et al. (1972).⁸ Only patients with carotid symptoms or "malignant" vertebro-basilar symptoms, i.e. motor defects or bilateral loss of vision, were considered for treatment. As the risk of cerebral infarction is highest during the months immediately after the first TIAs⁷ all patients were given AC treatment for 2 months combined with heparin infusion during the first days of treatment. Thereafter, they were randomized to either continue with the AC treatment (see below) or change to anti-platelet therapy. During the first 2 months 21 patients were excluded for several reasons; complete cerebral infarction (1 patient), bleeding complications usually due to heparin (8), operation with thromboendarterectomy (4), other diagnoses than the first one given (2), other intercurrent disorders (2), inability to manage the treatment (2), refusal to change from AC treatment to anti-platelet therapy (2). Six patients had TIA, but continued with the AC treatment. Thus, 135 patients remained for randomization. The number of patients, arterial territory, type of cerebral ischemia, treatment, age and sex are given in table 1. The time between the first TIA/RIND and the initial AC treatment is shown in table 2 and the number of TIAs/RIND for the treatment is given in table 3. The time between the last actual TIA/RIND and the AC treatment was usually only a few days. The frequency of hypertension, diabetes mellitus, hyperlipidemia, angina pectoris and previous cerebral and myocardial infarction are given in table 4. Except in the clinical investigation aiming to make a distinction between TIA and RIND and between the carotid and the vertebro-basilar territories, a lumbar puncture was performed in all patients in order to exclude intracranial hemorrhage or infection. CT scan was performed in 18 patients (13%) and an isotope brain scan in 4 patients (3%) in order to exclude a tumor or a small intracerebral hematoma.

Angiographic study was carried out on 47 patients

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TABLE 1 Age and Sex Distribution of Patients Treated Either With Anticoagulants (AC) or With Anti-platelet Therapy (ASA + DP) in Relation to Different Arterial Territories and the Type of Cerebrovascular Disorder

	Number	Age (mean)	Sex	Treatment	
				AC	ASA + DP
Carotid TIA	35	66 yr	20/15	16	19
Carotid RIND	62	68 yr	46/16	31	31
Vertebro-Basilar TIA	26	63 yr	17/9	14	12
Vertebro-Basilar RIND	12	68 yr	10/2	7	5
Total	135	66 yr	93/42	68	67

(35%) mostly in those with carotid TIA (43%). The angiographic study was done to find patients suitable for either carotid endarterectomy or an extra-intracranial bypass operation. Therefore, only patients in good general condition, usually below 65 years-of-age and without any history of cardiac disease or severe peripheral arterial insufficiency, were investigated. Mostly arch angiography was performed but in some cases only an arteriogram was done in the symptomatic carotid artery. The angiograms were normal in 14 patients (30%) and abnormal with local or generalized atheromata in 33 patients (70%).

The AC treatment given perorally with coumadin (AP[®] or Apekumarol[®]) was almost always started together with heparin infusion for 4–5 days (20 - 40 000 IU/day) adjusted according to the arterial thromboplastin time (APTT), which should not exceed 100 sec. The AC treatment was controlled with the TT-test, to a therapeutic range between 7–15% of the normal.⁹ The anti-platelet therapy was given with acetylsalicylic acid (ASA) (Premaspin[®] 0.5 g × 2) combined with dipyridamole (DP) (Persantine[®] 75 mg × 2). Patients randomized to anti-platelet therapy stopped AC treatment after 2 months and continued after 2 days with ASA + DP. These patients were regularly controlled by measuring the concentration of blood-salicylate. Values between 0–0.8 mmol/l were noted. Patients with new cerebral symptoms and blood-salicylate < 0.1 mmol/l were given higher doses of ASA + DP. After randomization, patients with AC treatment were followed 12.4 months per patient (range 3–19 months). Patients with anti-platelet therapy were followed 12.8 months (range 1–19 months). Some patients were excluded only a few months after the randomization.

TABLE 2 Time Between First TIA/RIND and Initial AC-Treatment

Arterial territory	Time			
	≤1 day	2–7 days	7–28 days	≥28 days
Carotid TIA (n = 35)	9 (25.7%)	5 (14.3%)	10 (28.6%)	11 (31.4%)
Carotid RIND (n = 62)	15 (24.2%)	28 (45.2%)	13 (21%)	4 (6.5%)
Vertebro-Basilar TIA (n = 26)	12 (46.2%)	4 (15.4%)	6 (23.1%)	4 (15.4%)
Vertebro RIND (n = 12)	2 (16.7%)	7 (58.3%)	2 (16.7%)	1 (8.3%)
Total	38 (28.1%)	44 (32.6%)	31 (23.0%)	20 (14.8%)

Results

The cerebro- and cardiovascular events and the bleeding complications after randomization are summarized in table 5. Completed cerebral infarctions occurred in 4 patients, i.e. 3% during one year. All these patients were men and earlier had had carotid TIA or RINDs. Only one completed cerebral infarction occurred during AC treatment. This was a 78-year-old man, who, 2 h after a myocardial infarction, had a complete right-sided hemiparesis. The other 3 complete cerebral infarctions occurred during anti-platelet therapy, in 2 patients within one month after the initial AC treatment and in one man after 6 months treatment with ASA + DP. One 56-year-old man had a lethal cerebral hemorrhage after 5 months AC treatment. He had a well regulated hypertension and the TT-value was 8%.

TABLE 3 Number of TIA/RIND Before the Start of the AC-treatment

Arterial territory	Number of TIA/RIND		
	1	2–4	≥5
Carotid TIA (n = 35)	13 (37.2%)	11 (31.4%)	11 (31.4%)
Carotid RIND (n = 62)	48 (77.4%)	13 (21.0%)	1 (1.6%)
Vertebro Basilar TIA (n = 26)	17 (65.4%)	6 (23.1%)	3 (11.5%)
Vertebro Basilar RIND (n = 12)	12 (100.0%)	—	—
Total	90 (66.6%)	30 (22.2%)	15 (11.1%)

TABLE 4 Frequency and Number of Patients with Hypertension, Manifest Diabetes Mellitus, Hyperlipidemia, Angina Pectoris and Previous Cerebral and Myocardial Infarctions

	AC-treatment (n = 68)	Anti-platelet therapy (n = 67)	Total (n = 135)
Hypertension	37 (54.4%)	28 (41.8%)	65 (48.1%)
Diabetes mellitus	13 (19.1%)	3 (4.5%)	16 (11.9%)
Hyperlipidemia	5 (7.4%)	3 (4.5%)	8 (5.9%)
Angina pectoris	6 (8.8%)	15 (22.4%)	21 (15.6%)
Previous myocardial infarction	5 (7.4%)	6 (9.0%)	11 (8.1%)
Previous cerebral infarction*	16 (23.5%)	9 (13.4%)	25 (18.5%)

*Earlier than 1 year before the present symptoms.

TABLE 5 Number of Cerebrovascular Disorders, Bleeding Complications and Lethal Myocardial Infarctions During AC-Treatment or Anti-Platelet Therapy After the Randomization

	TIA/RIND		Completed cerebral infarction		Cerebral hemorrhage		Lethal myocardial infarction		Bleeding complications	
	AC	ASA + DP	AC	ASA + DP	AC	ASA + DP	AC	ASA + DP	AC	ASA + DP
Carotid TIA (n = 35)	2	4	—	2	1	—	—	—	1	—
Carotid RIND (n = 62)	4	6	1	1	—	—	1	—	3	3
Vertebro-Basilar TIA (n = 26)	1	3	—	—	—	—	1	1	2	—
Vertebro-Basilar RIND (n = 12)	2	—	—	—	—	—	2	—	—	—
Total	9	13	1	3	1	—	4	1	6*	3**

*) hematuria (1) gluteal hematoma (1) hemoptysis (1) severe epistaxis (3).

**) bleeding ulcers (1) severe epistaxis (2).

Nine patients (6.7%) had TIA/RIND during AC treatment and 13 patients (9.6%) during anti-platelet therapy. Thus, 10 patients (7.4%) had ischemic signs during AC treatment and 16 patients (11.9%) during anti-platelet therapy. Bleeding complications, so severe that the patients had to enter the hospital were reported in 6 (8.8%) during AC treatment; hematuria (1 patient), hemoptysis (1), large gluteal hematoma (1) and epistaxis (3). In 2 patients the treatment had to be withdrawn, but was continued in the other patients after adjustment of the TT-values. Bleeding complications occurred in 3 patients (4.5%), during anti-platelet therapy, 2 had epistaxis and one patient had bleeding duodenal ulcers and had to halt treatment. Four patients had lethal myocardial infarctions during AC treatment but only one during anti-platelet therapy.

In all the patients who had cerebral infarctions treatment was withdrawn and they were not followed further. Four patients were excluded due to bleeding complications, including the one with a cerebral hemorrhage. Seven patients died during the investigation, 5 due to myocardial infarctions, one of pulmonary embolism and one of pulmonary malignancy. In 5 patients who had repeated TIAs or RIND, the treatment was changed from AC to ASA + DP in one and from ASA + DP to AC in 4. Three patients stopped the AC treatment in connection with an operation or due to inability to manage the medication, and the anti-platelet therapy was withdrawn in 3 patients due to gastrointestinal disturbances and allergic reactions. Altogether, 13 patients in every treatment group had to be excluded during the observation time due to different reasons, 3 caused by cerebrovascular diseases during AC treatment, and 7 during anti-platelet therapy. A survey of the causes of exclusion and the time relation to the randomization is given in table 6.

All cerebral infarctions occurred in men, whereas TIA/RIND also were seen in women (table 7). The relation of all cerebrovascular events between men and women was 2.9:1 whereas the sex difference between men and women in the study was 2.2:1. The sex distribution of the myocardial infarctions was 4:1.

The TIA/RIND appeared during the AC treatment, usually when the TT-test was within "ther-

apeutic" levels, i.e. between 7–15%. TIA/RIND during anti-platelet therapy appeared more often when the concentration of blood-salicylate was low.

Discussion

The natural history of TIA has been studied in several investigations and 25–40% of the patients had a cerebral infarction within 5 years after the first TIA.^{10–14} The risk is also believed by some to be higher after TIA with symptoms in the carotid territory than in the vertebro-basilar territory.¹⁵ The risk is also higher during the first year and especially during the first 2 months after the onset of TIA.^{7, 14} Studies of the natural history of RIND are sparse but Loeb et al. (1978)¹⁶ have followed patients with transient ischemic attacks and patients with reversible symptoms of longer duration without finding any clinical or prognostic difference, except that TIA had a stronger tendency to recur than RIND. This was also seen in

TABLE 6 Causes and Number of Patients Who Were Excluded From the Investigation After Randomization.

	AC (n = 68)		ASA + DP (n = 67)	
	No.	Time after randomization	No.	Time after randomization
TIA/RIND	1	5 months	4	1,4,10,11 months
Completed cerebral infarction	1	6 months	3	1,1,6 months
Cerebral hemorrhage	1	3 months	—	
Lethal myocardial infarction	4	5,8,8,11 months	1	4 months
Other deaths*	1	13 months	1	12 months
Severe bleeding** complications 2**	7,12 months	13*	2 months	
Other complications 34*	7,7,9 months	35*	1,4,13 months	
Total	13		13	

x) pulmonary infarction (1) malignancy (1).

xx) hematuria (1) gluteal hematomas (1).

xxx) bleeding ulcers (1).

xxxx) inability to cooperate (2) gall bladder operation (1)

xxxxx) allergy against ASA (1) gastrointestinal disturbances (2)

TABLE 7 Sex Distribution of Patients Having Cerebrovascular Disorders or Lethal Myocardial Infarction During AC-Treatment or Anti-Platelet Therapy After Randomization

	TIA/RIND		Completed cerebral infarction		Cerebral hemorrhage		Lethal myocardial infarction	
	AC	ASA + DP	AC	ASA + DP	AC	ASA + DP	AC	ASA + DP
Carotid TIA								
men (n = 20)	1	2	—	2	1	—	—	—
women (n = 15)	1	2	—	—	—	—	—	—
Carotid RIND								
men (n = 46)	3	5	1	1	—	—	1	—
women (n = 16)	1	1	—	—	—	—	—	—
Vertebro-Basilar TIA								
men (n = 17)	—	3	—	—	—	—	—	1
women (n = 9)	1	—	—	—	—	—	1	—
Vertebro-Basilar RIND								
men (n = 10)	1	—	—	—	—	—	2	—
women (n = 2)	1	—	—	—	—	—	—	—
Total								
men (n = 93)	5	10	1	3	1	—	3	1
women (n = 42)	4	3	—	—	—	—	1	—

our study, where almost all patients with RIND had only one attack, whereas more than 50% of the TIA patients had 2 or more attacks before the treatment was instituted (table 3). Therefore, the time was longer between the first actual TIA and the start of the AC treatment than between the first RIND and the treatment (table 2). In fact, more than 2/3 of the RIND patients had received AC treatment within one week after the first symptoms whereas less than 50% of the TIA patients had started the treatment within one week (table 2). Patients with a longer time between the treatment and their first actual TIA/RIND had usually not sought medical care until their symptoms had reappeared with increased frequency and intensity. However, within one month almost 90% of the patients had started AC treatment.

The AC treatment was given to all patients during the initial 2 months. Owing to this, the most dangerous period⁷ was protected with a therapy proved useful against cerebral infarction in patients with TIA.^{4, 10, 17-19} Whisnant *et al.* (1973)¹⁴ recommended a treatment for at least 1-2 months, but, according to our own experience, several patients, especially those with carotid symptoms, need much longer treatment.⁴

As there is a risk of bleeding complications during AC treatment and a need for regular controls of the prothrombin time, we started this investigation to see if an initial AC treatment could be replaced by anti-platelet therapy, i.e. by agents which inhibit the first steps of thrombus formation by inhibiting adhesion and aggregation of the platelets. The best known drug is ASA which achieves its antithrombotic effect by blocking the conversion of arachidonic acid to pharmacologically active prostaglandins (for review see Samuelsson 1977).²⁰ Most other anti-inflammatory

drugs affect the aggregation of platelets as do other substances such as sulfinpyrazone, clofibrate and dipyridamole. Dipyridamole (DP) decreases platelet adhesion and aggregation²¹ but probably in a somewhat different way than ASA by potentiating the action of endogenous prostacyclin.²²

DP only was tested in 1969 by Acheson *et al.*²³ in a double-blind study against placebo in 169 patients with different reversible ischemic strokes. No prophylactic effect against cerebral infarction was found, even in as high doses as 400 mg and 800 mg daily.

ASA was tested in 1971 by Harrison *et al.*²⁴ on 2 patients with amaurosis fugax and they found a decrease of the frequency. Dyken *et al.* (1973)²⁵ found no effect of ASA on 15 TIA patients treated with 600 mg ASA daily compared with 11 control patients giving placebo. Neither could Field *et al.* (1977)⁵ find any significant difference in occurrence of deaths or cerebral infarctions in patients treated either with 1.3 g ASA daily or placebo, whereas a significant reduction of TIAs could be seen in patients receiving ASA. The Canadian cooperative study⁶ showed a prophylactic effect of ASA against cerebral infarction in men having had TIA, but not in women.

In our study we have used a combination of ASA and DP which has been proved to have effect on patients with arterial thromboembolism.²⁶ However, the effect seems to be dose-dependent. Doses of ASA up to 1 g daily increases the bleeding time whereas it decreases with higher doses.²⁷ In rabbits the most synergistic anti-thrombotic effect has been found by a combination of DP (2 mg/kg) and ASA (12 mg/kg).²⁸ Therefore, we have used 1 g ASA in combination with 150 mg of DP daily, except in some patients where low blood concentrations of salicylate were found when new cerebral ischemic symptoms appeared.²⁹

During the present investigation 7 patients had completed strokes (4.5%), one ischemic and one hemorrhagic during the initial 2 month AC treatment, and 4 ischemic and one hemorrhagic strokes after the randomization. The frequency of hemorrhagic strokes (1.3%) is about that seen during the natural history of TIA^{10, 30} and need not necessarily be caused by the anti-coagulant treatment. The frequency of completed ischemic strokes (3.2%) during the investigation is about 10 times lower than the expected during the first year after TIA^{7, 14} and corresponds to results found earlier.⁴

After the randomization at 2 months there was no significant difference between patients with AC treatment and patients with anti-platelet therapy. Three completed cerebral infarctions were seen in patients receiving ASA + DP against one in the AC-treated patients. All these strokes appeared in men, who earlier had had symptoms from the carotid territory. Three of them were between 73 and 78 years of age and one of them, receiving AC treatment, had a cerebral infarction 2 hours after a myocardial infarction, 8 months after the first cerebral symptoms. The fourth patient was 56-years-old with long-standing hypertension who initially had repeated TIAs with paresis of his right arm. He was free of symptoms during the initial AC treatment but had a complete left-sided hemiparesis while playing golf 2 weeks after change to ASA + DP. Four vessel cerebral angiography showed occlusion of the right internal carotid artery and a stenosis of the left internal carotid artery. Therefore, possibly hemodynamic mechanisms caused at least 2 of the cerebral infarctions.

The present investigation has shown that it is possible to continue the protection against cerebral infarctions in patients with TIA/RIND by giving anti-platelet therapy with ASA and DP after an introductory AC treatment of about 3 months, which recently also has been suggested by Sandok et al. (1978).³¹ This may decrease the risk of bleeding complications which are associated with AC treatment. Anti-platelet therapy is rather safe but not entirely free from complications as shown in our study. The effect of acetylsalicylic acid restricted only to men, which was reported from the Canadian cooperative study,⁶ could not be confirmed in our investigation. It remains to be proved if anti-platelet therapy can be given to all TIA/RIND patients from the beginning, directly after the first ischemic symptoms, thereby omitting an initial AC treatment. As the etiology of TIA/RIND is still incompletely understood it is also possible that one therapy is more appropriate in some patients while the other therapy is better in others. Platelet and coagulation studies in patients with cerebral ischemia may clarify this question.

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Addendum

Since this manuscript was submitted a 2-year follow

up was completed. This provides additional support for the AC treatment ($\chi^2 = 4.92$; $0.01 < p < 0.05$). Ischemic cerebral symptoms (TIA, RIND, infarctions) occurred in 8 patients during AC treatment as opposed to 22 patients treated with ASA + DP ($\chi^2 = 12.27$; $p < 0.001$). On the other hand, bleeding complications were more frequent during AC treatment (including 2 lethal hemorrhages) than during anti-platelet therapy. These results strengthen our opinion that a short AC treatment during the first critical period (3–12 months) after the initial ischemic symptoms is preferable, followed by the safer but less effective anti-platelet drugs as a long-term prophylactic treatment in patients with TIA/RIND.

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Plasma Acetylsalicylate and Salicylate and Platelet Cyclooxygenase Activity Following Plain and Enteric-Coated Aspirin

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SUMMARY Compressed and enteric-coated acetylsalicylate (ASA) tablets have been compared in normal healthy subjects. Plasma ASA and salicylate (SA) were measured by high pressure liquid chromatography (HPLC). Platelet cyclooxygenase activity *in vitro* was studied by a radiometric technique. Following ingestion of 650 mg of ASA in the form of compressed tablets, cyclooxygenase activity was inhibited 95% within 45 min. Enzyme activity was observed to increase within 8 h and reached 10% of control level by 24 h. The pattern suggests that only circulating platelets are affected by ASA ingestion. Following the administration of 650 mg of ASA as enteric-coated tablets comparable inhibition of cyclooxygenase activity was observed, although the effect was delayed, reflecting the delayed appearance of ASA in the plasma. Return to control levels followed a pattern similar to that observed with the compressed tablet.

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ACETYLSALICYLATE (ASA) REDUCES the frequency of transient ischemic attacks and lowers the incidence of stroke and death in patients with cerebral vascular disease.^{1, 2} A number of aspects of the clinical pharmacology of this commonly used drug require further investigation. The use of enteric-coated ASA may reduce the incidence of gastrointestinal side effects. The efficacy of such a preparation as an antiplatelet agent has not been studied. Since the mechanisms of the antithrombotic effect of ASA is believed to be the inhibition of platelet cyclooxygenase activity,³ it may be useful to compare the drug preparations with respect to inhibition of this enzyme activity. A large scale clinical trial to establish the

efficacy of enteric-coated ASA in patients with cerebral vascular disease is probably unnecessary if an appropriate degree of enzyme inhibition is demonstrated.

The optimal dosage schedule for ASA also is uncertain. Clinical trials in which efficacy of ASA has been demonstrated both in patients with cerebral vascular disease^{1, 2} and venous thrombosis⁴ have used a q.i.d. regimen. Since the effect of a dose of ASA on platelets is irreversible,⁵ it is possible that less frequent administration would constitute equally effective antiplatelet therapy. New platelets enter the circulation at a rate which approximates 10% of the circulating pool per day. If megakaryocytes are affected by ASA in such a way that the platelets formed and released subsequent to a dose of ASA have nonfunctional cyclooxygenase, less frequent dosage may be required than if ASA inhibits only circulating platelets. We have measured the cyclooxygenase activity of platelets over a period which includes the first 24 h after ASA ingestion. We also measured plasma ASA and salicylate (SA) levels following ingestion of plain and enteric-coated ASA to investigate whether plasma

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