

Aspirin Plus Coumarin Versus Aspirin Alone in the Prevention of Reocclusion After Fibrinolysis for Acute Myocardial Infarction

Results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial

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Background—Despite the use of aspirin, reocclusion of the infarct-related artery occurs in $\approx 30\%$ of patients within the first year after successful fibrinolysis, with impaired clinical outcome. This study sought to assess the impact of a prolonged anticoagulation regimen as adjunctive to aspirin in the prevention of reocclusion and recurrent ischemic events after fibrinolysis for ST-elevation myocardial infarction.

Methods and Results—At coronary angiography <48 hours after fibrinolytic therapy, 308 patients receiving aspirin and intravenous heparin had a patent infarct-related artery (Thrombolysis In Myocardial Infarction [TIMI] grade 3 flow). They were randomly assigned to standard heparinization and continuation of aspirin alone or to a 3-month combination of aspirin with moderate-intensity coumarin, including continued heparinization until a target international normalized ratio (INR) of 2.0 to 3.0. Angiographic and clinical follow-up were assessed at 3 months. Median INR was 2.6 (25 to 75th percentiles 2.1 to 3.1). Reocclusion (\leq TIMI grade 2 flow) was observed in 15% of patients receiving aspirin and coumarin compared with 28% in those receiving aspirin alone (relative risk [RR], 0.55; 95% CI 0.33 to 0.90; $P<0.02$). TIMI grade 0 to 1 flow rates were 9% and 20%, respectively (RR, 0.46; 95% CI, 0.24 to 0.89; $P<0.02$). Survival rates free from reinfarction and revascularization were 86% and 66%, respectively ($P<0.01$). Bleeding (TIMI major and minor) was infrequent: 5% versus 3% ($P=NS$).

Conclusions—As adjunctive to aspirin, a 3-month-regimen of moderate-intensity coumarin, including heparinization until the target INR is reached, markedly reduces reocclusion and recurrent events after successful fibrinolysis. This conceptual study provides a mechanistic rationale to further investigate the role of prolonged anticoagulation after fibrinolytic therapy. (*Circulation*. 2002;106:659-665.)

Key Words: fibrinolysis ■ anticoagulants ■ aspirin

With the introduction of fibrinolytic therapy, survival after ST-elevation myocardial infarction has been shown to largely depend on early restoration of coronary patency.¹

Recurrent ischemic events are often attributed to reocclusion of the infarct-related artery.^{2,3} Reocclusion is a time-dependent phenomenon,⁴ which is seen in $\approx 10\%$ of patients at the time of discharge,⁵ with an incidence of up to $\approx 30\%$ in the first year, despite the use of aspirin.^{6,7} Previous studies have demonstrated a 2-fold increased risk of death in the case of early reocclusion after successful thrombolysis² and a higher risk of reinfarction and recurrent ischemic events in both the short term and the long term.³ Even in the absence of clinical reinfarction, reocclusion has been shown to preclude

recovery of left ventricular function,⁸ the most important determinant of prognosis after myocardial infarction. Prevention of reocclusion is therefore warranted.

Although aspirin has become the standard antithrombotic therapy, oral anticoagulation has also been shown markedly effective in coronary artery disease.⁹ In patients with non-ST-elevation acute coronary syndromes,⁹⁻¹¹ a combined regimen of antiplatelet and anticoagulation therapy seemed promising.

It was therefore hypothesized that outcome after ST-elevation myocardial infarction could be improved by a prolonged adjunctive anticoagulation regimen of 3 months of moderate-intensity coumarin, including intravenous heparinization until an international normalized ratio (INR) of 2.0

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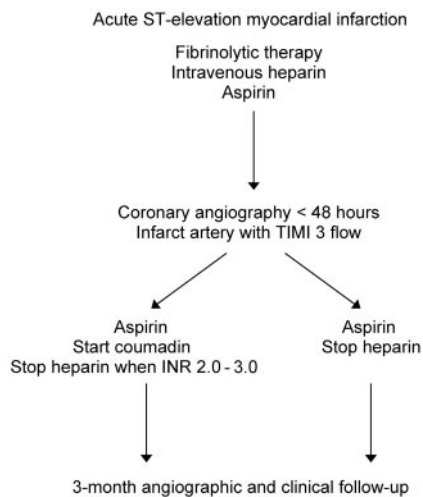


Figure 1. Design of the study.

to 3.0 when compared with standard anticoagulation as adjunctive to fibrinolysis and aspirin. The Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis (APRICOT)-2 trial sought to assess the efficacy of this prolonged combined antithrombotic regimen in the prevention of reocclusion and recurrent ischemic events in patients with a patent infarct artery after fibrinolytic therapy for suspected acute myocardial infarction.

Methods

Study Protocol

The APRICOT-2 trial was an investigator-initiated, open-label, randomized angiographic and clinical follow-up study performed in 7 centers in the Netherlands between 1994 and 2000 (Figure 1). Patients with chest pain ≥ 30 minutes and ≤ 6 hours, refractory to nitrates, were treated with fibrinolytic therapy in the case of ST-elevation ≥ 0.2 mV in ≥ 2 contiguous precordial leads or ≥ 0.1 mV in ≥ 2 limb leads. The agents used were anistreplase (30 U in 5 minutes), streptokinase (1.5 million units in 30 to 60 minutes), reteplase (2 bolus doses of 10 U, 30 minutes apart), or accelerated recombinant tissue-type plasminogen activator (r-TPA).¹ Patients received a starting dose of 160 mg aspirin, followed by 80 mg once daily. Adjunctive intravenous unfractionated heparin (UFH) was given for 48 hours. An intravenous bolus of 5000 U was followed by an infusion of 24,000 U/24 hours, with a target activated partial thromboplastin time of twice the control. After fibrinolytic therapy, patients with clinical and/or ECG signs of reperfusion who were clinically stable were asked for informed consent. In the case of participation, coronary angiography had to be performed within 48 hours after the start of fibrinolytic therapy.

Patients were eligible to enter the study if the local investigator assessed the flow in the infarct-related artery as Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow.¹² By telephone service, patients were allocated to one of two treatments by block randomization, stratified per center. In one arm, the patient continued the daily use of 80 mg of aspirin, and heparin was discontinued at 48 hours. In the other arm, coumadin was started in addition to 80 mg of aspirin, and heparin was continued until moderate-intensity anticoagulation was achieved, with a target INR between 2.0 and 3.0.

Follow-up angiography was scheduled at 3 months. Clinical follow-up, including bleeding complications, was collected until the second angiography. By protocol, an ischemia-guided revascularization strategy was followed.⁶ If angioplasty was performed before the scheduled follow-up angiography, the patency status of the infarct-related artery before dilation was considered the angiographic

follow-up end point. The study was approved by the ethics review boards of the participating hospitals.

Exclusion Criteria

Patients older than 75 years, those with a contraindication to antithrombotic therapy, and those with a bypass graft as the infarct-related vessel were not eligible. Patients with a culprit stenosis that had previously been dilated were not included, and patients with left main stem stenosis or an unidentifiable culprit lesion were not included.

Coronary Angiography

The infarct-related artery was identified by correlating the coronary anatomy with the distribution of wall motion abnormality on the 30° right anterior oblique and 60° left anterior oblique ventriculograms. This information was combined with the distribution of ST-elevation on the admission ECG. If applicable, lead V₄R was used for discrimination between the circumflex artery and the right coronary artery as the infarct-related artery.⁶

TIMI flow grading¹² and quantitative coronary angiographic assessment were performed at a core laboratory (Heartcore Leiden B.V., Leiden, the Netherlands), each by a different reader blinded to the assigned strategy. The optimal single-plane projection was selected that identified the culprit stenosis in its greatest severity, with minimal foreshortening or overlapping of branches, and end-diastolic frames were chosen for quantitative angiographic analysis.

Study End Points

The primary end point was reocclusion of the infarct-related artery at angiographic follow-up, defined as TIMI grade 2 flow or less: TIMI grades 0 and 1 flow representing anatomic reocclusion, and TIMI grade 2 flow functional reocclusion, as patients were included with good antegrade flow (TIMI grade 3 flow).

The secondary end point was event-free survival: a clinical course without death, reinfarction, or revascularization. Mortality refers to death of all causes. Reinfarction was defined with use of the Global Utilization of Streptokinase and TPA for Occluded coronary arteries (GUSTO)-1 trial criteria. At least 3 of the 4 criteria were required to qualify for reinfarction.¹³ As a safety end point, TIMI major and minor bleeding is reported.¹⁴

Statistical Analysis

Sample Size

In the APRICOT-1 trial, reocclusion occurred in 25% of patients allocated to aspirin, according to the European Cooperative Study Group criteria (ECSG; grading 4 and 5).⁷ For the present study, we anticipated a similar rate of TIMI grade 0 to 1 flow (ECSG grade 5) as in the APRICOT-1 aspirin arm (20%). Based on differences in definition, the incidence of TIMI grade 2 flow was expected to be higher than the observed 5% of ECSG grade 4 in APRICOT-1. The estimated incidence of reocclusion for APRICOT-2 was therefore set at 30%. The trial was designed to have 80% power to demonstrate a relative reduction of 50% in the incidence of reocclusion, with a 2-sided α of 5%. This would require 266 patients with angiographic follow-up. In the APRICOT-1 study, 87% of patients underwent both angiographies.⁷ Therefore, the target for this study was set at 305 patients. Stopping rules were not formally prespecified. Death, reinfarction, and major hemorrhage were reported to the principal investigator at 100 and 200 randomly assigned patients. At his discretion, the trial could be prematurely discontinued.

Analysis

Continuous variables were compared by the Student's *t* test or the Mann-Whitney *U* test, whenever appropriate. For comparisons between discrete variables, the χ^2 test and Fisher's exact probability test were used. Analyses were performed according to the intention-to-treat principle.

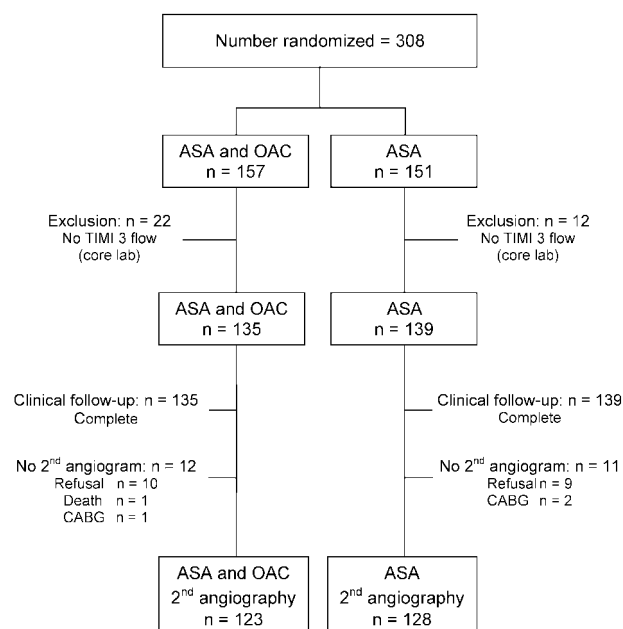


Figure 2. Flow chart showing number of patients excluded and number remaining per treatment group with clinical and angiographic follow-up. ASA indicates aspirin; OAC, oral anticoagulation.

Results

In total, 308 patients were randomly assigned, of whom 34 (11%) were excluded from analysis because flow in the infarct artery was not considered TIMI grade 3 flow by the core laboratory. Follow-up angiograms of the patients with TIMI grade 2 flow at inclusion angiography were not routinely analyzed.

Clinical and angiographic baseline characteristics of the remaining 274 patients were similar to those of the 308 patients. Clinical follow-up was complete for all patients with adjudicated TIMI grade 3 flow after fibrinolysis. Fibrin-specific agents (reteplase, r-TPA) were used in 44% of patients allocated to the prolonged, combined antithrombotic regimen (59 of 135) and in 36% of those receiving the standard antithrombotic regimen (50 of 139; $P=NS$).

Angiographic follow-up was available in 251 of the 274 patients (92%). After initial consent, 19 patients (7%) refused to undergo the second angiography. Other reasons for not undergoing follow-up angiography are given in Figure 2. Baseline characteristics of patients with and without a second angiogram were not different.

Table 1 shows the baseline characteristics at the time of study entry. The treatment groups were well balanced.

Antithrombotic Medication

After the start of coumarin, heparin was continued until the target INR (2.0 to 3.0) was reached. Consequently, heparinization lasted 66 hours longer in patients allocated to the combined antithrombotic regimen, when compared with patients randomly assigned to standard heparinization and the use of aspirin alone: 110 versus 44 hours ($P<0.01$). In 9 of 135 patients (7%), the target INR was not reached during hospitalization. Overall, heparin was discontinued in 16 patients (12%), although adequate oral anticoagulation had not (yet) been achieved. The median INR during follow-up was 2.6 (25 to 75th percentiles 2.1 to 3.1).

Sixteen patients (12%) randomly assigned to aspirin and coumarin did not receive the assigned antithrombotic medication (Figure 3). Three of these refused follow-up angiography.

TABLE 1. Clinical and Angiographic Characteristics at Study Entry

	Aspirin and Coumarin (n=135)	Aspirin (n=139)
Men	111 (82)	112 (81)
Age, y	57±11	58±10
Previous MI	15 (11)	17 (12)
Current smoker	82 (61)	77 (55)
Diabetes	8 (6)	9 (6)
Hypertension	31 (23)	43 (31)
Cholesterol ≥5.0 mmol/L	79 (59)	86 (62)
Time to thrombolysis, h	2.3±1.3	2.4±1.4
Median peak CK, U/L (25th–75th percentiles)	1034 (388–2202)	861 (496–1825)
Thrombolysis to first angio, h	30±14	31±15
Infarct-related artery		
LAD	59 (44)	52 (37)
LCx	14 (10)	27 (19)
RCA	62 (46)	60 (43)
Single-vessel disease	75 (56)	75 (54)
Culprit stenosis severity, QCA, %	57±15	59±13

MI indicates myocardial infarction; CK, creatine kinase; LAD, left anterior descending artery; LCx, left circumflex coronary artery; RCA, right coronary artery; and QCA, quantitative coronary angiography.

Data are presented as number (%) of subjects for discrete variables and as mean±SD for continuous variables except for peak CK value.

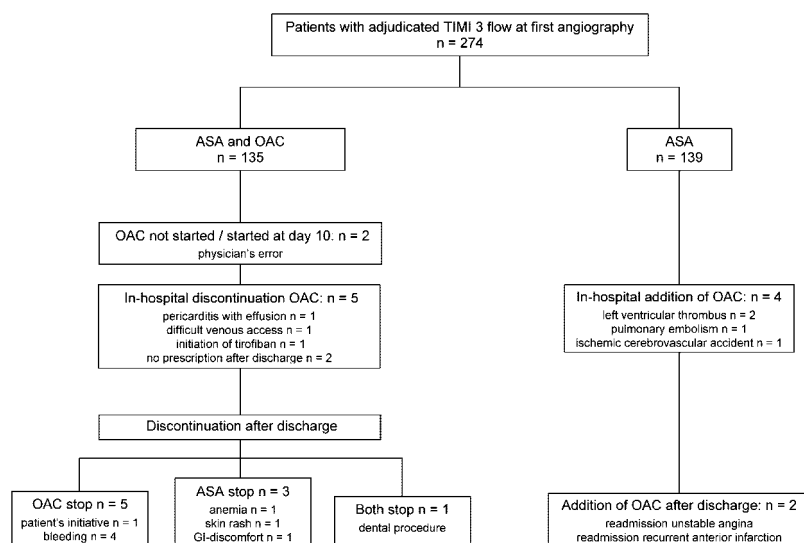


Figure 3. Changes in assigned anti-thrombotic medication after random assignment. ASA indicates aspirin; OAC, oral anticoagulation; GI, gastrointestinal.

raphy, in the other 13 patients, 3 reocclusions (23%) were observed. Six patients (4%) allocated to aspirin alone received additional coumarin during follow-up (Figure 3). Two of these refused angiographic follow-up; the others had TIMI grade 3 flow at the second coronary angiography. None of the patients allocated to the standard antithrombotic regimen discontinued aspirin before follow-up angiography.

Reocclusion

Figure 4 shows the primary outcome as assessed by the core laboratory. In patients allocated to aspirin and coumarin, reocclusion was observed in 19 of 123 patients (15%), compared with 36 of 128 (28%) in patients receiving aspirin alone (relative risk [RR], 0.55; 95% CI, 0.33 to 0.90, $P<0.02$). This difference is mainly caused by a reduction in the incidence of TIMI grade 0 to 1 flow: 11 of 123 (9%) versus 25 of 128 (20%) (RR, 0.46; 95% CI, 0.24 to 0.89; $P<0.02$). Reocclusion rate for the fibrin-specific lytics was 17%; for the non-fibrin-specific agents it was 24% ($P=NS$). No interaction between the fibrin specificity of the lytic and the allocated antithrombotic regimen was observed (Breslow-Day, $P=0.56$).

Clinical Outcome

Table 2 shows the secondary end points. Event-free survival was significantly higher in patients allocated to aspirin and coumarin compared with those in the aspirin alone arm.

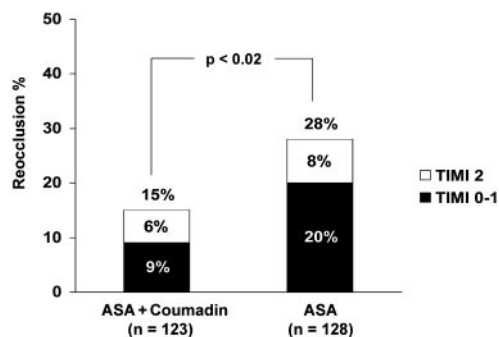


Figure 4. Incidence of reocclusion at follow-up angiography.

Patients on the combined antithrombotic regimen had a significantly lower reinfarction rate. Of interest, in the aspirin alone group, 6 of the 11 reinfarctions occurred after discharge, against 1 of the 3 reinfarctions on the combined regimen. Both in-hospital reinfarctions in the combination group occurred during continued heparinization while the target INR had not yet been reached. Of the 5 in-hospital reinfarctions in the aspirin alone group, 4 occurred within 24 hours of discontinuation of intravenous heparin.

The lower number of patients with a revascularization in the combination group was primarily caused before discharge: 5 of 135 (4%) versus 27 of 139 (19%) ($P<0.01$). One patient in the aspirin alone arm underwent CABG after an unsuccessful urgent angioplasty. Procedure-related infarctions were seen in 3 patients allocated to the standard antithrombotic regimen and in none of those allocated to the combined regimen. From the time of random assignment,

TABLE 2. Clinical Outcome Until 3-Month Follow-Up Angiography

	Aspirin and Coumarin (n=135)	Aspirin (n=139)
Death	1	0
Reinfarction	3 (2)	11 (8)†
In hospital	2	5
After discharge	1	6
Revascularization	17 (13)	43 (31)‡
In hospital		
PTCA	5	25
CABG	0	3
After discharge		
PTCA	11	14
CABG	1	2
Event-free survival	116 (86)	92 (66)*

Data are presented as number of subjects and proportion (%) per treatment group. Patients may have had events in more than one category. Reinfarctions presented are not procedure-related (see text).

* $P<0.01$; † $P<0.05$; ‡ $P<0.01$.

patients allocated to aspirin alone were discharged after 8 days and those receiving the combined regimen after 9 days ($P=NS$).

Bleeding

Bleeding complications according to the TIMI criteria occurred in 7 patients (5%) in the combination treatment group (2 major, 5 minor) and 4 (3%) in the aspirin alone group (2 major, 2 minor; $P=NS$). No cerebral bleeding was reported in either group. In each group, 1 patient (1%) underwent blood transfusion.

Discussion

APRICOT-2 is the largest randomized study to date with both clinical and angiographic follow-up addressing the efficacy of a continuous, combined antithrombotic regimen up to 3 months after ST-elevation myocardial infarction. The current findings in patients with an open infarct-related artery after fibrinolytic therapy are in concordance with a smaller angiographic study in a more heterogeneous population.¹⁰ In the present study, an antithrombotic regimen of aspirin, prolonged heparinization, and 3 months of moderate-intensity coumarin conferred a 45% relative reduction in reocclusion as compared with standard heparinization and the use of aspirin alone.

Heparin and Aspirin in Acute Myocardial Infarction

The introduction of aspirin has markedly improved clinical and angiographic outcome after fibrinolytic therapy.^{5,15} With it, the routine use of subcutaneous UFH only conferred a modest additional clinical benefit, which was lost early after discharge.^{16,17} The limited data regarding adjunctive intravenous UFH do not suggest an important clinical benefit^{17,18} despite a suggested beneficial effect on patency and reocclusion in different settings.

With conventional administration of 3 to 6 hours of r-TPA, adjunctive intravenous UFH did not result in higher 90-minute patency,¹⁹ yet an effect on 7- to 120-hour patency has been demonstrated.^{20,21} With regard to streptokinase, the GUSTO-1 angiographic trial did not demonstrate an effect of intravenous UFH on 90-minute patency; the impact on 24-hour patency remains unknown in lack of a placebo-controlled comparison. The best 5- to 7-day angiographic outcome after streptokinase was observed with adjunctive intravenous UFH, with comparable patency and reocclusion rates to r-TPA and intravenous UFH.¹

In view of the above, the APRICOT-2 protocol mandated that all patients received adjunctive intravenous UFH, irrespective of the fibrinolytic agent; this was to exclude selection bias through a potential effect on patency at the time of inclusion angiography. For patients allocated to receive coumarin, heparin was continued until the target INR (2.0 to 3.0) was reached. Consequently, patients in the coumarin arm received intravenous heparin for an additional 2½ days when compared with patients in the aspirin alone arm. This design ensured a continuous, combined antithrombotic regimen. How much prolonged heparinization in itself has contributed to the observed effect on reocclusion and reinfarction is

beyond the scope of this trial and cannot be determined in this design.

Adjunctive intravenous UFH carries the potential risk of a rebound after its discontinuation, which continuous, prolonged anticoagulation with coumarin might prevent. Interestingly, the majority of in-hospital reinfarctions in the aspirin alone group were seen within 24 hours after discontinuation of intravenous heparin, suggesting a rebound phenomenon, as observed in the GUSTO-1 trial.²² In previous trials, anticoagulation until discharge with either subcutaneous UFH¹⁶ or the low-molecular-weight-heparin (LMWH) dalteparin²³ showed a promising in-hospital clinical benefit, which dissipated within 1 month after discontinuation. These observations and the fact that in the present study at least half of the observed difference in reinfarction was realized after discharge support a beneficial effect of prolonged anticoagulation with coumarin (Table 2). As stated before, reocclusion is a time-dependent phenomenon, with TIMI flow grade 0 to 1 rates of $\approx 10\%$ at discharge⁴ and 20% at 3 months in patients using aspirin.⁶ Even after demonstrated patency, at 4 weeks, reocclusion occurs in $\approx 25\%$ of patients within 1 year.⁷ Although longer heparinization may account for part of the early benefit, the continued use of oral anticoagulation after discharge seems pivotal to prevent a rebound in recurrent ischemic events and additional reocclusions.

Coumarin and Aspirin in Acute Myocardial Infarction

Dose-adjusted, frequently monitored, and individually tailored therapy is a prerequisite for optimal oral anticoagulation therapy, with both safety and efficacy depending on the intensity of treatment.^{9,24} Compliance is another important aspect, which has recently been shown to vary per country and hospital, markedly affecting efficacy.¹¹ The large trials studying the addition of lower-intensity anticoagulation to aspirin such as Coumadin Aspirin Reinfarction Study (CARS)²⁵ (fixed-dose warfarin [1 or 3 mg/d], mean INRs 1.1 and 1.6) and Combined Hemotherapy and Mortality Prevention Study (CHAMP)²⁶ (dose-adjusted, mean INR 1.8) reported more bleeding but did not demonstrate a clinical benefit. However, the smaller APRICOT-2 and Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT)-2 trials²⁷ with mean INRs well above 2.0 showed improved clinical outcome. Moreover, compliance in the present study was high, with 88% of patients assigned to the combined antithrombotic regimen treated according to the protocol.

As far as inferences to daily clinical practice are concerned, this trial does not represent the general population with myocardial infarction: eligible when clinically stable, younger than 75 years, and TIMI grade 3 flow as inclusion criteria. A similar consideration holds true for the low bleeding rates in this study,²⁴ in combination with the rather stringent TIMI bleeding criteria.¹⁴ However, the larger ASPECT-2 (mean INR 2.4)²⁷ and Warfarin-Aspirin Reinfarction Study (WARIS)-2 (mean INR 2.2)²⁴ trials, which refer to a broader population, also reported benefit from the addition of oral anticoagulation with acceptable safety. A second Scandinavian trial is Low Dose Anticoagulation and ASA

Study (LOWASA) (aspirin versus aspirin plus oral anticoagulation, INR 1.0 to 1.5), which is still running and designed to include 5000 patients. In aggregate, these trials will provide a more reliable risk-benefit estimation, although the available evidence to date seems promising.²⁴

Implications

With the continuing search toward earlier reperfusion in a higher proportion of patients, prevention of subsequent reocclusion has inherently become an even more important issue.²⁸ In view of the interindividual and intraindividual variability in anticoagulation with both heparin and coumarin, other agents might prove more efficacious, be it through a more predictable effect, more profound impact on the coagulation cascade, or simply better compliance. Two large angiographic trials, the Heparin-Aspirin Reperfusion Trial (HART)-2²⁹ and Acute Myocardial Infarction-Streptokinase (AMI-SK),²⁴ showed promising findings by using LMWHs after fibrinolysis. Of note, in the trials suggesting that LMWHs (ASessment of the Safety and Efficacy of a New Thrombolytic [ASSENT]-PLUS,²³ ASSENT-3^{29a}) or direct Xa-inhibition (synthetic PENTasaccharide as an Adjunct to fibrinoLYsis in ST-Elevation acute myocardial infarction [PENTALYSE]^{29b}) are superior to UFH, administration of the new agents was continued for several days after discontinuation of intravenous heparin in the anchor arm. This in contrast to the Hirulog Early Reperfusion or Occlusion (HERO)-2 trial, in which bivalirudin administered for a similar duration as intravenous UFH resulted in lower reinfarction rates after streptokinase.³⁰ Whereas coumarin requires regular monitoring, these agents do not, and oral direct thrombin inhibitors have recently seen the light. In anticipation of follow-up studies with the aforementioned agents, the implementation of long-term therapy with coumarin could be facilitated through self-assessed dose-adjusted anticoagulation.²⁴

Whether a routine revascularization strategy in this study population could positively influence reocclusion and associated events remains to be determined. The available evidence to date does not support such an aggressive approach.³¹ This explains the symptom-driven, ischemia-guided revascularization strategy in this trial, irrespective of the presence of a severe stenosis at baseline angiography. Although the 3-month TIMI grade 0 to 1 flow rate of 9% on the combined antithrombotic regimen seems to compare favorably with the rates observed after primary PTCA with or without stenting,³² it should be realized that the current study group is much more selected. With the improved techniques and use of glycoprotein IIb/IIIa receptor blockers, reevaluation of the impact of a routine invasive strategy after successful thrombolysis seems warranted.

Limitations

Because this trial was investigator-initiated and performed in an era of various consecutive large, sponsored reperfusion trials, inclusion took 6 years, which also accounts for the different types of lytics that have been used over the years. Although the observed clinical benefit seems promising, the present study is limited by its open design, sample size, and

selected population. The trial was designed and powered as an angiographic study, with blind assessment of the primary end point. With clinical outcome as secondary end point, it should be considered a conceptual study, which provides insight into the mechanism underlying a potential clinical benefit.

Conclusions

The APRICOT-2 findings strongly suggest that a continuous, prolonged antithrombotic regimen of both antiplatelet and anticoagulation therapy has additional impact after fibrinolytic therapy. This was achieved with an acceptable safety in a high compliance setting. With respect to the implications for daily clinical practice, the results of larger trials on this and other combined antithrombotic regimens will have to be awaited.

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Aspirin Plus Coumarin Versus Aspirin Alone in the Prevention of Reocclusion After Fibrinolysis for Acute Myocardial Infarction: Results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial

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