

Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction

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When published in 1980, this study represented the largest experience gained with coronary angiography performed during the very acute phase of an evolving ST-segment elevation myocardial infarction. It included 322 patients representative of 1210 patients admitted for an acute myocardial infarction during the period of recruitment from March 1971 until December 1978. A signed informed consent was obtained from patients, which explained the nature of the research and potential benefits in selecting the best treatment, which could include coronary artery bypass surgery.

The study population was relatively young, only 6.2% of patients being older than 65 years; 80% were male and 20% female. Subgroups were formed according to time from onset of symptoms to performance of angiography from 0 to 4 hours, 4 to 6 hours, 6 to 12 hours, and 12 to 24 hours, each group comprising 126, 82, 57, and 57 patients, respectively. The angiographic findings were classified as total coronary occlusion in the absence of forward flow of contrast material in the involved coronary artery, and as subtotal occlusion when more than 95% narrowing was found by visual inspection.

The proportion of patients with total occlusion was highest in the group catheterized early, 87.3%, and decreased subsequently to 85.3% between 4 and 6 hours, 68.4% between 6 and 12 hours, and 64.9% between 12 to 24 hours. Following angiography, 79 patients underwent emergency surgical revascularization. A thrombus was retrieved by Fogarty catheter in 72% of these patients, 88% of those with an angiographic image suggestive of a thrombus, and 25% of those without such an image. The recovered thrombus contained variable quantities of acute inflammatory cells and a thickened layer of fibrin and platelets interspersed with red cells in its middle portion, creating a layering effect. The authors concluded that total coronary occlusion is frequent during the early hours of ST-segment elevation myocardial infarction and that the frequency decreased in the following 24 hours, suggesting that coronary spasm or thrombus formation with subsequent recanalization or both

could be important in the evolution of infarction. They did not take into account the frequency of subtotal occlusion, which would likely correspond to TIMI grade 1 and 2 flow according to the more dynamic TIMI grade flow classification now used. The proportions of patients with subtotal occlusion in the study increased during the initial 24 hours. Combining the patients with total and subtotal occlusion yielded a frequency of total or near-total occlusion of 97.6% in the first 4 hours, 96.2% between 4 and 6 hours, 85.9% between 6 and 12 hours, and 70.7% between 12 and 24 hours. These figures are in line with our actual understanding that a thrombus is present in practically all patients, with subsequent spontaneous reperfusion in a certain number. A complication rate of 10.8% was reported with the procedure: nonfatal ventricular fibrillation in 30 cases, intramyocardial injection of dye in 1 patient, disruption of a nonculprit plaque in 2 patients, and 2 fatalities. Transient hypotension was observed in 29 patients.

This study was performed before the era of balloon angioplasty. Controversies then existed on the exact etiology of myocardial infarction; coronary spasm was seen by many as the major contributor to plaque disruption, followed by thrombus formation by blood flow stasis. It was also a time of changes in concepts and attitudes. Reports were already coming out in the literature on intracoronary instillation of nitroglycerin and of streptokinase. This study by DeWood et al contributed to the revolution that occurred in the following years in the management of ST-segment myocardial infarction.

1980

The Polish government legalizes the independent trade union Solidarnosc; Paris bomb blast kills 4 and injures 12 at a Jewish synagogue; and release of Martin Scorsese's film "Raging Bull" with Robert de Niro as the boxer Jake LaMotta



Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction

ISIS-2 (Second International Study of Infarct Survival) Collaborative Group

Lancet. 1988;2:349-360

The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico (GISSI) and Second International Study of Infarct Survival (ISIS-2) trials were two landmark trials that were decisive for the worldwide introduction of thrombolysis as standard therapy for acute myocardial infarction. ISIS 2, in addition, convincingly showed the benefit of aspirin used alone or in combination with streptokinase in reducing cardiac death.

The GISSI trial (*Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico [GISSI]*). *Lancet*. 1986;1:397-402) was an open-label study that enrolled 11 806 patients from 171 coronary care units. Patients admitted within 12 hours after the onset of symptoms and with no contraindications to streptokinase were randomized to receive streptokinase in addition to usual treatment. Overall mortality at 21 days was reduced from 13.0% in controls to 10.7% with streptokinase (relative risk [RR] 0.81, $P=0.0002$).

ISIS-2 enrolled 17 187 patients from 417 hospitals up to 24 hours after the onset of suspected acute myocardial infarction. Patients were randomized double-blind to: (i) a 1-hour IV infusion of 1.5 MU of streptokinase; (ii) 1 month of 160 mg/day enteric-coated aspirin; (iii) both active treatments; or (iv) neither. Streptokinase reduced the 5-week vascular mortality from 12.0% to 9.2% (odds reduction: 25%, $P<0.00001$), and aspirin from 11.8% to 9.4% (odds reduction: 23%, $P<0.00001$). The individual effects of each drug appeared to be additive, with 8.0% vascular death with the combination and 13.2% with neither drug. Aspirin significantly reduced nonfatal reinfarction (1.0% vs 2.0%) and nonfatal stroke (0.3% vs 0.6%). An excess of nonfatal reinfarction was reported when streptokinase was used alone, but this appeared to be entirely avoided by the addition of aspirin.

The trial validated the use of an antiplatelet therapy as primary care in acute myocardial infarction and as adjunctive antithrombotic therapy to thrombolysis. Given the

safety, ease of administration, and low cost of aspirin, the results were rapidly extrapolated to all acute ischemic syndromes, including non-ST-segment elevation myocardial infarction and unstable angina. Aspirin, since this trial, is first-line therapy in these syndromes. Prompt administration is recommended when an acute coronary syndrome is suspected, although a relationship between time of administration and benefit had not been documented in ISIS-2, as was the case for streptokinase. Prehospital administration is also widely practiced. The benefits of aspirin with streptokinase were also extrapolated to thrombolytic agents other than streptokinase and have stimulated research for more effective adjunctive therapy.

Since, all clinically effective anticoagulants and antiplatelet drugs have been tested as adjunctive therapy to thrombolysis. Heparin failed to show a favorable risk-benefit ratio. Heparin is routinely used with tissue plasminogen activator, and optionally with streptokinase. Many recent studies, although of small sample sizes, showed a clear gain with enoxaparin over unfractionated heparin when combined with either tissue plasminogen activator (tPA), streptokinase, reteplase or tenecteplase (TNKase). GP IIb/IIIa (GP, glycoprotein) antagonists combined with half-dose reteplase and TNKase were also shown to be very effective, but associated with a significant increase in the risk of bleeding that precludes their routine use. Clopidogrel in combination with aspirin is currently under investigation.

1988

UN Peacekeeping Forces receive
Nobel Peace Prize;
200th anniversary of the birth of
Arthur Schopenhauer, the profoundly pessimistic
German philosopher; and US Navy cruiser
"Vincennes" mistakenly shoots down
Iran Air A300 Airbus, killing 290 persons

Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients

Antiplatelet Trialists' Collaboration

BMJ. 1994;308:71-77, 81-106

The extensive collaborative overview carried out by R. Collins, R. Peto, and C. Baigent from Oxford, and by P. Sandercock, D. Dunbabin, and C. Warlow from Edinburgh had a major impact on the use of antiplatelet therapy worldwide, mainly of aspirin. It will last as a classic piece of work. The analysis included more than 100 000 individuals from 145 randomized trials performed before March 1990 of prolonged antiplatelet therapy versus controls, and 29 randomized comparisons between antiplatelet regimens.

All risk categories combined, antiplatelet therapy reduced events by about 25%. In the heterogeneous groups of trials and patients, the benefits were apparent irrespective of age, gender, blood pressure, and the presence or absence of diabetes. Treatment of high-risk patients reduced by one third the risk of nonfatal myocardial infarction, by one third the risk stroke, and by one sixth the risk of vascular death. Treatment of 1000 patients with acute myocardial infarction prevented 40 vascular events over 1 month, and that of patients with unstable angina prevented 50 events over 6 months. The benefit in low-risk individuals without a previous vascular event was less apparent, possibly because of a low overall incidence. Nevertheless, treatment in about 28 000 individuals resulted in a statistically significant reduction of 5 per 1000 in nonfatal myocardial infarction and of 2 per 1000 in nonfatal stroke, with no effect on survival.

The main conclusions drawn by the authors of the meta-analyses were that: (i) antiplatelet therapy protected a wider range of patients at risk than previously treated; (ii) it should be considered for almost all with suspected acute myocardial infarction, unstable angina, or a history of myocardial infarction, angina, stroke, transient ischemic attack, arterial bypass surgery, or angioplasty; and (iii) medium-dose aspirin (75-325 mg/day) was the treatment most widely used, while no other regimen appeared significantly more effective in preventing myocardial infarction, stroke, or death. The authors recommended lifelong therapy in the absence of contraindications, although the duration of observation in trials averaged 2 years. The gain with treat-

ment across a wide range of patients and the power of the analysis were strong incentives to wide application and to further research on antiplatelet treatment.

The meta-analysis was recently updated to include 212 000 individuals from trials performed up to September 1997. Among these, 135 000 subjects had been enrolled in trials comparing antiplatelet therapy with controls, and 77 000 were from trials comparing different antiplatelet regimens. The trials added reinforce the data in acute stroke and in certain chronic conditions such as atrial fibrillation and peripheral vascular disease, and provide new data on different doses of aspirin and different antiplatelet agents.

The 1994 meta-analysis had a ratio of comparison trials to control trials of 0.2 (29/145). The ratio rose in 1997 to 0.5 (93 comparison trials and 194 control trials), reflecting a major shift in clinical practice and clinical research over a short period of time. Not only have new agents been introduced into clinical practice, but combination therapy is also increasingly used. Thus, a combination of aspirin, clopidogrel, and a glycoprotein (GP) IIb/IIIa receptor antagonist is routinely prescribed in stent implantation procedures, and the combination clopidogrel aspirin is gaining wide acceptance in high-risk patients.

1994

Cesar Romero, US actor best known for playing “The Joker” in the cult television “Batman” series, dies, aged 86; ice skater Nancy Kerrigan is attacked with a crowbar by Tonya Harding’s bodyguard during practice for the US Championship; and 34 die, and \$7 billion damage is caused, when a major earthquake rocks Los Angeles



A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease (ESSENCE)

M. Cohen, C. Demers, E. P. Gurfinkel, A. G. Turpie, G. J. Fromell, S. Goodman, A. Langer, R. M. Califf, K. A. Fox, J. Premmereur, F. Bigonzi, J. Stephens, B. Weatherley, and the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group (ESSENCE)

N Engl J Med. 1997;337:447-452

The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) Study Group directly compared enoxaparin with unfractionated heparin in 3171 patients with a non-ST-segment elevation acute coronary syndrome. Previous studies had independently shown the efficacy of unfractionated heparin in these syndromes as well as the efficacy of low-molecular-weight heparin (LMWH) against placebo.

The entry criteria in the ESSENCE trial were: (i) angina at rest of recent onset lasting at least 10 minutes and occurring within hours before randomization, with evidence of underlying coronary disease manifested by either ST-segment shift or T-wave changes in two contiguous leads; (ii) previous myocardial infarction (MI) or revascularization procedure; or (iii) ischemic heart disease suggested by the results of noninvasive or invasive testing. These criteria did not specifically identify a particularly high-risk category of patients. Enoxaparin, 1 mg/kg SC q 12 hours, or IV unfractionated heparin, 5000 U bolus, followed by an infusion titrated to an activated partial thromboplastin time (aPTT) of 55 to 85 seconds, were administered double-blind. All patients received aspirin. The study drugs were administered for a minimum of 48 hours and up to a maximum of 8 days. The median duration of treatment was 2.6 days in both groups. Enoxaparin was discontinued before percutaneous procedure or coronary artery bypass surgery, to be replaced with unfractionated heparin. The primary outcome of death, MI, or recurrent angina at 14 days occurred in 16.6% of enoxaparin patients and 19.8% of unfractionated heparin patients (odds ratio [OR] 0.8, $P=0.02$) and the composite end point of death or MI in 14.3% and 17.4% of patients (NS), respectively. At 30 days, the triple end point occurred in 19.8% and 23.3% of patients, respectively (OR 0.81, $P=0.02$) and the end point of death or MI in 16.8% and 19.6% of patients, respectively (NS). The need for revascularization at 30 days was significantly less frequent among patients assigned to enoxaparin than among those assigned to unfractionated heparin (27% vs 32.2%, $P=0.001$). A subsequently published 1-year follow-up of patients showed maintained benefit. No significant differ-

ences existed in the risk of major bleeding between both groups, with rates of 6.5% with enoxaparin and 7.0% with unfractionated heparin. Minor bleeding, however, occurred more frequently with enoxaparin (11.9% vs 7.2%). Cost-effectiveness analyses were favorable to enoxaparin.

The ESSENCE trial was therefore successful in showing that the advantages of LMWH over unfractionated heparin could translate into clinical benefit in patients with an acute coronary syndrome. These advantages are a more predictable anticoagulation response allowing subcutaneous administration with no need for monitoring, a higher ratio of inhibition (factor Xa/thrombin), less platelet effect, and less heparin-induced thrombocytopenia. Subsequently, three other trials compared an LMWH and unfractionated heparin in similar populations. One of the trials tested enoxaparin and showed benefits in the same range as those observed in the ESSENCE trial. The two others trials tested different formulations of LMWH and could not show a gain over unfractionated heparin. The long-term use of enoxaparin after hospital discharge resulted in no benefit, but in excess bleeding. Favorable results have been obtained with LMWHs as adjunctive therapy to thrombolysis in patients with ST-segment elevation MI.

1997

Cathy Freeman of Australia wins the world 400-meter title, becoming the first athlete of Aboriginal descent to win a gold medal in the Championships; India celebrates 50 years of independence from British rule; and Diana, Princess of Wales, and her companion, Dodi Fayad, are tragically killed in a car crash in Paris

Aspirin, heparin, or both to treat acute unstable angina

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N Engl J Med. 1988;319:1105-1111

Patients with unstable angina were included in this randomized, double-blind, 2×2 factorial trial to study the usefulness of aspirin, heparin, and their combination. A total of 479 patients were randomized as soon as possible after hospital admission and within 24 hours after the last episode of pain. Doses of aspirin of 650 mg daily were used and heparin was administered as a bolus of 5000 units followed by an infusion titrated to an activated partial thromboplastin time (aPTT) of 1.5 to 2 times control values. Coronary angiography was performed in the majority of patients a mean of 4 days after randomization. End points were assessed when the final decision for patient orientation to medical management, percutaneous intervention, or coronary artery bypass surgery had been made.

The study drugs were administered for a mean of 6 days. Refractory angina, myocardial infarction, or death occurred in 22.9%, 11.9, and 1.7% of patients, respectively, in the placebo group. The rates were significantly reduced in the three treatment arms, to 3.3% with aspirin ($P=0.01$), 0.8% with heparin ($P<0.0001$), and 1.6% with the combination treatment ($P=0.01$), respectively. The two deaths that occurred in the study were in the placebo group. The number of patients who experienced a fatal or nonfatal myocardial infarction was reduced from 14 in the placebo group to 4, 1, and 2 patients, respectively, in the active treatment groups. Myocardial infarction was less often associated with a Q-wave in patients treated with active drug compared with patients receiving placebo (86% vs 29%, $P<0.01$) and accompanied by lesser peak creatine kinase (CK) elevation. Only heparin significantly reduced the occurrence of refractory angina, from 31% of patients receiving placebo to 9.7% of patients receiving heparin alone or in combination with aspirin. Aspirin resulted in a trend to a reduction, with an incidence of refractory angina of 17%. Bleeding complications in the trial were mainly related to cardiac catheterization, and in excess only with the administration of heparin with or without aspirin.

The study, despite the limitations of a small sample size and a composite end point, assessed short-term, promoted

the use of antithrombotic in clinical practice for the management of acute coronary syndromes. It came at a time when a need for more intensive management of patients with unstable angina was becoming apparent. The results of the Second International Study of Infarct Survival (ISIS-2) trial were published the same year, and thrombolysis for the management of ST-segment elevation myocardial infarction was being generalized. Two trials had previously documented the usefulness of aspirin initiated during the subacute phase of unstable angina and one randomized trial had suggested that heparin could be efficacious.

Since, the acute coronary syndromes have become a platform for the evaluation of new antithrombotic drugs. Thrombolysis failed to show a benefit despite some angiographic improvement. Low-molecular-weight heparins have been successfully introduced in clinical practice, and hirudin has shown greater efficacy than heparin during the acute phase. Glycoprotein (GP) IIb/IIIa receptor antagonists have also been introduced for the management of high-risk patients and patients undergoing a percutaneous procedure. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial recently documented an additive gain when clopidogrel was added to aspirin compared with aspirin alone; patients were administered heparin in the trial.

1988

The Latvian flag is raised in Riga for
the first time since the annexation by the USSR;
Ferdinand and Imelda Marcos are indicted
on racketeering charges;
and Naguib Mahfouz becomes the first
Arab writer to win the Nobel prize for literature



The prognostic value of serum troponin T in unstable angina

C. W. Hamm, J. Ravkilde, W. Gerhardt, P. Jorgensen, E. Peheim, L. Ljungdahl,
B. Goldmann, H. A. Katus

N Engl J Med. 1992;327:146-150

This seminal paper was the first to describe the diagnostic value of troponin T in patients with unstable angina. It further explored whether its detection in the circulation might be a useful predictor of prognosis. The study included 109 consecutive patients hospitalized in four European centers. At admission, diagnosis of acute myocardial infarction was an exclusion criterion, including creatine kinase (CK) activity 200 U/L or more, as well as a myocardial infarction within the previous 2 weeks. Blood samplings were obtained within 6 hours of admission and every 8 hours thereafter for 48 hours.

Patients were categorized using the Braunwald classification into class 1 (severe or accelerated angina of new onset), class 2 (angina at rest not active within the previous 48 hours), and class 3 (angina at rest within the previous 48 hours). All therapeutic decisions were made without knowledge of troponin T levels.

All 25 patients with class 1 and class 2 angina had normal total CK, CK-MB (membrane-bound) activity, and troponin T values at admission and during the 48-hour sampling period. They also showed no ECG changes and had no cardiac events. In contrast, an elevation in troponin T was seen in 33 of the 84 patients with class 3 angina (39%). Noteworthy was that the elevation was seen early and was of modest amplitude, with median values of 0.50 $\mu\text{g/L}$, (range 0.20-3.63 $\mu\text{g/L}$). It was present at admission or in the second sampling in 84% of patients; in the other patients it occurred after repeated episodes of chest pain in-hospital. CK-MB activity was elevated in 4% of patients. ECG changes were present in 78% of the patients with negative troponin T values and in 85% of those with positive values. Coronary angioplasty and bypass surgery were performed as frequently in patients with elevated and normal troponin T levels. Thirty percent of patients with elevated levels experienced myocardial infarction with ST-segment elevation within 2 to 10 days after admission and 15% died. One patient with no elevation had a myocardial infarction (MI) and died. Thus, elevated troponin T levels preceded 10 out of the 11 myocardial infarctions (3 occurred perioperatively) and 5

of the 6 fatalities (3 after coronary artery bypass grafting), yielding a positive predictive value of 30% and a negative predictive value of 98%.

The study, so small it was, was a landmark observation that changed our management approach to acute coronary syndromes. Numerous observations from various investigators have since confirmed the high frequency of troponin T or troponin I elevation in patients with an acute coronary syndrome as well as the impaired prognosis associated with an elevation. On the other hand, the favorable prognosis observed in patients with no elevation permits more appropriate management. The assessment of troponin levels is now the most important tool for decision-making besides clinical evaluation. Its value adds to other markers of risk including the ECG, CK-MB levels, Holter monitoring, and the exercise test. Importantly, the test has become a marker of the underlying pathophysiology and, accordingly, a help for treatment selection. Elevated troponin levels reflect cell necrosis associated with an ongoing intracoronary thrombotic process. In large MI with concomitant CK-MB elevation, the thrombus is most likely occlusive; in smaller MI with normal or only mildly elevated MI, cell necrosis is likely caused by distal embolization of thrombogenic material. These patients profit most from an intensive antithrombotic therapy, as was documented with low-molecular-weight heparins and GP IIb/IIIa receptor antagonists. They also profit from an aggressive management strategy that includes revascularization procedures.

1992

25th Olympic Summer games open in
Barcelona, Spain; General Manuel Noriega of
Panama is sentenced to 40 years in prison
for drug trafficking; and Vaclav Havel resigns as
Czechoslovakian president after a proclamation of
sovereignty by the Slovak Parliament

Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty

The EPIC Investigators

N Engl J Med. 1994;330:956-961

EPIC (Evaluation of IIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications) was the first large-scale placebo-controlled trial ever performed with a glycoprotein (GP) IIb/IIIa receptor antagonist (the monoclonal antibody abciximab). The drug was initiated in the catheterization laboratory before coronary angioplasty. A total of 2099 patients at high-risk of complications due to severe unstable angina, evolving myocardial infarction (MI), or complex plaque characteristics were enrolled. (These situations are particularly appropriate to test a potent antagonist to platelet aggregation.) The patients were randomized to placebo, abciximab as a bolus, or abciximab as a bolus followed by a 12-hour infusion. The primary end point at 30 days was a composite of death, nonfatal MI, and the need for unplanned interventions, including surgery, repeated percutaneous revascularization, stent implantation, and intra-aortic balloon counterpulsation. As compared with placebo, the bolus and infusion dose of abciximab reduced the risk of an adverse outcome event by 35% (8.3% vs 12.3%, $P=0.008$). The risk reductions were in the same range for the end points of unplanned procedures and MI, and were consistent across the various subgroups analyzed. Most events in the placebo group occurred within 6 hours after the procedure. With the bolus, events were delayed for several hours, corresponding to the time of maximal occupancy of the receptor, and were not statistically different from those occurring in the placebo group after 30 days.

Abciximab was associated with a doubling of hemorrhagic events and bleeding events that required administration of blood products. Major bleeding occurred in 7% of placebo patients, 11% of abciximab bolus, and 14% of abciximab bolus followed by infusion. In the latter group, 15% of patients received red cell transfusions and 6% platelet transfusions. Bleeding occurred mainly at arterial punctures sites and was a frequent complication in coronary artery bypass surgery.

Despite the excess bleeding, the drug was approved for clinical use based on the efficacy results. The bleeding risk was largely controlled in subsequent studies by the admin-

istration of lower doses of heparin and its early discontinuation after procedures, and by withdrawing vascular sheaths after a few hours when the activated partial thromboplastin time (aPTT) values were back to near control values (Evaluation of PTCA to Improve Long-term Outcome by c7E3 GPIIb/IIIa receptor blockade [EPILOG] trial). The usefulness of abciximab was also subsequently documented in patients with refractory unstable angina submitted to angioplasty within the following 24 hours (Chimeric 7E3 AntiPlatelet in Unstable angina REfractory to standard treatment [CAPTURE] trial), patients undergoing an elective percutaneous procedure (EPILOG trial), or stent implantation (Evaluation of Platelet IIb/IIIa Inhibitor for STENTING trial [EPiSTENT] trial). The Global Use of Streptokinase and Tissue plasminogen activator for Occluded arteries (GUSTO-IV) trial failed, however, to show a benefit of the drug in patients with a non-ST-segment elevation acute coronary syndrome managed medically; in the Global Use of Strategies To open Occluded arteries in acute myocardial infarction (GUSTO-V) trial that included patients with ST-segment elevation MI, no reduction in mortality was shown with the combination of full-dose abciximab and half-dose reteplase. Abciximab remains indicated in patients with ST-elevation MI when a primary intervention is indicated. In the ADMIRAL study (Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up), the prompt administration of abciximab before referral to the catheterization laboratory for primary stenting resulted in better TIMI 3 grade flow before the intervention, after the intervention, and after 6 months, as well as in a marked reduction in event rates.

1994

Ex-US president Richard Nixon dies
after a stroke, aged 81; US scientists discover the
top quark, the missing atomic component;
and hundreds of thousands die in two weeks
of tribal slaughter in Rwanda



Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators

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N Engl J Med. 1999;340:1623-1629

The study tested the hypothesis that abciximab will be particularly effective in patients with elevated troponin T levels, a surrogate marker of thrombus formation, because of the properties of the glycoprotein (GP) IIb/IIIa receptor antagonist to block platelet aggregate formation. For this purpose, the authors assessed the value of troponin T levels that were collected at baseline in the Chimeric 7E3 Anti-Platelet in Unstable angina REfractory to standard treatment (CAPTURE) trial to predict the benefit of abciximab. The double-blind randomized trial compared abciximab with placebo in 1265 patients with refractory unstable angina. The patients were randomized in the trial after the angiographic identification of a culprit lesion suitable for percutaneous revascularization. The interventions were performed 18 to 24 hours after randomization. Cardiac events were monitored during a 6-month follow-up period. Patients with a recent myocardial infarction were excluded from the present study since troponin levels can remain elevated in blood for many days after a myocardial infarction.

Baseline troponin T values below the cutoff value of 0.1 ng/mL or less were found in 69.1% of patients. Among these patients, the rates of death or myocardial infarction were similar with abciximab treatment and with placebo. They occurred during the phase of medical management before angioplasty in 1.0% and 0.7% of patients, at 1-month in 5.2% and 4.9%, and at 6 months in 9.4% and 7.5% of patients, respectively. Among the 31.9% of patients with values >0.1 ng/mL, abciximab significantly reduced the rates of death or myocardial infarction. The rates were 0.7% and 6.6% ($P=0.02$) before angioplasty, 5.8% and 19.6% ($P=0.002$) at 30 days, and 9.5% and 23.9% ($P=0.002$) at 6 months, respectively. Abciximab, therefore, reduced the risk of an event in patients with elevated troponin T levels to that of patients with troponin T levels below the diagnostic cutoff values. The reduction was present before as well as after the revascularization procedure and maintained over a period of 6 months.

Creatine kinase, myocardial band (CK-MB) values were elevated at baseline in 13% of patients. An elevation was

a significant predictor of increased risk at all time points. However, regression analysis, which included interaction with treatment, indicated no relation between the benefit of abciximab and the CK-MB level. The same absence of interaction was seen with ST-segment depression and T-wave inversion.

The study nicely correlated the mechanisms of action of the drug with the pathophysiology of the disease and with the clinical benefit. The benefit extended to medical management as well as to reperfusion procedures. The elevation of troponin T is believed to represent distal embolization of thrombotic material that can occur spontaneously and that can be provoked by catheter manipulation, balloon inflation, and stent deployment. The study further defined modalities for optimal benefit of treatment in patients with an acute coronary syndrome. Indeed, the main study revealed that the early gain and the gain at 30 days with abciximab were not maintained after 6 months. The present study showed that treatment of 100 patients with elevated troponin T prevents 15 cases of death or myocardial at 6 months. Similar results have been published with dalteparin, showing that the benefit of treatment was mainly confined to patients with elevated troponin T levels.

1999

British actor Oliver Read dies of a heart attack while drinking in a bar; a US expedition to Everest finds the body of British climber George Mallory, missing for 70 years—the find fails to resolve the question of whether he was the first to conquer the mountain; and Yugoslavian president Slobodan Milosevic becomes the first serving head of state to be indicted as a war criminal



Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators

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N Engl J Med. 2001;345:494-502

CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) is a randomized double-blind trial comparing the combination of clopidogrel and aspirin with aspirin alone among 12 562 patients with a non-ST-segment elevation acute coronary syndrome (ACS). The inclusion criteria, which were refined to higher-risk patients during the recruitment period, included compatible symptoms plus the presence of ischemic ST-T changes or an elevation of the cardiac markers to two times or more the upper limit of normal. Patients were randomized within 24 hours of the last episode of chest pain and administered the study drugs for 3 to 12 months. A bolus dose of 300 mg clopidogrel was administered first, followed by 75 mg/day. The doses of aspirin were between 75 and 325 mg/day.

The study had two primary end points, the first was composed of cardiovascular death, myocardial infarction, or stroke and the second of the same components plus refractory ischemia. The first primary end point occurred at 30 days in 11.47% of the patients in the placebo group and 9.3% patients in the clopidogrel group (relative risk [RR] 0.80, $P=0.00005$), and the second, in 19% and 16.7% of patients, respectively (RR 0.86, $P=0.0004$). The benefit of clopidogrel emerged early after randomization, with risk reductions of 20% and 26% observed 24 hours after randomization for the two primary end points. The benefit continued long-term with an additional risk reduction from day 30 to 12 months. All subgroup analyses showed a 15% to 25% risk reduction favoring clopidogrel. There was significant excess in rates of major bleeding with the combination therapy (3.6% vs 2.7%, $P=0.003$), including life-threatening bleeding (2.1% vs 1.8%, $P=0.27$), minor bleeding (15.3% vs 8.6%, $P<0.0001$), and number of patients administered two or more blood units (2.8% vs 2.2%, $P<0.03$). Thrombocytopenia and neutropenia were infrequent and not in excess with clopidogrel.

The excess bleeding is of concern, but consistent with the greater antiplatelet effects and clinical benefit of the combination. Indeed, the efficacy of clopidogrel and ticlopidine had been previously well documented in numerous placebo-

controlled trials. Ticlopidine was further shown to be slightly superior to aspirin for the secondary prevention of stroke, while clopidogrel was superior to aspirin in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial for the prevention of vascular events in patients with recent stroke, recent myocardial infarction, and patients with symptomatic peripheral vascular disease. On the other hand, there was clinical evidence of added benefit with combined antiplatelet therapy. Thus, the combination of aspirin and a glycoprotein (GP) IIb/IIIa receptor antagonist is used in ACS, the combination of aspirin, clopidogrel, and a GP IIb/IIIa receptor antagonist is used in coronary stenting, and the combination aspirin and dipyridamole is used in stroke. Clopidogrel should clearly be preferred over ticlopidine, because it does not possess the serious adverse events of the latter. It is also well tolerated in a bolus dose, which is required for rapid antiplatelet effect.

The impressive results of the CURE trial mandate an evaluation of the combination therapy against other drug therapies that have been shown useful in ACS, such as the GP IIb/IIIa receptor antagonists, enoxaparin, and hirudin. They are also incentives to evaluate other combination therapies. Beyond the results and beyond the constraints of the protocol, the CURE trial showed the appropriateness of the concept that blocking platelets through different pathways of activation has the potential to magnify the clinical gain. The aspirin-clopidogrel combination may now be a new standard for the management of acute thrombotic situations as well as for secondary prevention in selected high-risk patients. The hypotheses need clinical testing.

2001

A Palestinian suicide bomber kills 8 people and injures about 100 in a Jerusalem restaurant; violence erupts following the seizure of white-owned farms in Zimbabwe; and Larry Adler, the world's best-known exponent of the mouth organ, dies aged 87



Multiple complex coronary plaques in patients with acute myocardial infarction

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This study shares analogies with the one by DeWood et al previously discussed. Both studies were descriptive of angiographic findings obtained in small series of patients with ST-segment elevation myocardial infarction. The two were published in the same journal, but 20 years apart. The first established the importance in clinical practice of thrombus formation in causing the infarction and contributed to a profound change in the therapeutic approach. The study by Goldstein et al provided a different perspective on the mechanisms of acute coronary syndromes by showing clinicians angiographic images of a diffuse disease, beyond the concept of a single culprit lesion that has influenced our practice for years. We are now learning that the disease is inflammation, which can have multiple etiologies, including risk factors and infectious or autoimmune processes, and which degrades plaques and leads to thrombus formation and myocardial infarction.

The authors examined the coronary angiograms of 253 patients with acute myocardial infarction for the presence of complex plaques at sites other than the infarcted-related lesion. The exact timing of the angiogram with regard to onset of chest pain is not stated. Plaques with 50% or more lumen diameter reduction at quantitative analysis were scrutinized for the presence of an intraluminal filling defect, ulcerations, irregularities, or impaired distal flow. The presence of two or more of these features defined a complex plaque. The plaques were considered anatomically remote from the main culprit lesion when located in a different artery, or a different branch, or located at least 5 cm away from the main lesion with an intervening disease-free segment. Patients with single and multiple complex plaques had the same demographic characteristics, risk factors, and previous cardiac history. A single complex plaque was identified in 60.5% of patients, and multiple complex plaques in 39.5%. Among the patients with multiple plaques, 83% had 2 and 17% had 3 or more complex plaques. The severity of stenosis of these secondary complex plaques tended to be less than in the infarct-related plaque, yet distal flow was impaired in 27% of cases. Patients with complex plaques more often required urgent bypass sur-

gery in-hospital (27% vs 5.2%); they also experienced more frequently in the following year a recurrent acute coronary syndrome episode (19.0% vs 2.6%) and underwent more often repeated angioplasty (32% vs 12.4%), particularly of non-infarct-related lesions (17% vs 4.6%), and coronary-artery bypass graft surgery (35% vs 11.1%). Multivariate analysis showed that the presence of multiple complex lesions was the strongest predictor of a complicated course.

These observations are in line with the autopsy findings of numerous ruptured plaques and of thrombus located at various sites in patients dying suddenly from a cardiac cause. The observations also help to explain the rapid angiographic progression in the severity of the disease frequently seen in patients with unstable angina.

A new era in investigation and management is already present: reliable markers of thrombosis and inflammation are available, such as troponin T and I levels and C-reactive protein, while work is being done on identifying new markers and new visualization methods of the complex plaque at risk of an event. Noninvasive methods are particularly appealing as they permit large-scale applicability. Potent antithrombotic drugs and potent drugs like statins, which stabilize the active atherosclerotic plaque, are available, and new therapies are emerging at an accelerating pace.

2000

Denmark votes to not adopt the single European currency; Pierre Trudeau, former Canadian prime minister, dies of prostate cancer, aged 80; and British rower Steve Redgrave becomes the first man to win five gold medals in consecutive Olympics in an endurance event