

The New England Journal of Medicine

Copyright © 2002 by the Massachusetts Medical Society

VOLUME 347

OCTOBER 24, 2002

NUMBER 17



ASPIRIN AND MORTALITY FROM CORONARY BYPASS SURGERY

DENNIS T. MANGANO, PH.D., M.D., FOR THE MULTICENTER STUDY OF PERIOPERATIVE ISCHEMIA RESEARCH GROUP*

ABSTRACT

Background There is no therapy known to reduce the risk of complications or death after coronary bypass surgery. Because platelet activation constitutes a pivotal mechanism for injury in patients with atherosclerosis, we assessed whether early treatment with aspirin could improve survival after coronary bypass surgery.

Methods At 70 centers in 17 countries, we prospectively studied 5065 patients undergoing coronary bypass surgery, of whom 5022 survived the first 48 hours after surgery. We gathered data on 7500 variables per patient and adjudicated outcomes centrally. The primary focus was to discern the relation between early aspirin use and fatal and nonfatal outcomes.

Results During hospitalization, 164 patients died (3.2 percent), and 812 others (16.0 percent) had nonfatal cardiac, cerebral, renal, or gastrointestinal ischemic complications. Among patients who received aspirin (up to 650 mg) within 48 hours after revascularization, subsequent mortality was 1.3 percent (40 of 2999 patients), as compared with 4.0 percent among those who did not receive aspirin during this period (81 of 2023, $P < 0.001$). Aspirin therapy was associated with a 48 percent reduction in the incidence of myocardial infarction (2.8 percent vs. 5.4 percent, $P < 0.001$), a 50 percent reduction in the incidence of stroke (1.3 percent vs. 2.6 percent, $P = 0.01$), a 74 percent reduction in the incidence of renal failure (0.9 percent vs. 3.4 percent, $P < 0.001$), and a 62 percent reduction in the incidence of bowel infarction (0.3 percent vs. 0.8 percent, $P = 0.01$). Multivariate analysis showed that no other factor or medication was independently associated with reduced rates of these outcomes and that the risk of hemorrhage, gastritis, infection, or impaired wound healing was not increased with aspirin use (odds ratio for these adverse events, 0.63; 95 percent confidence interval, 0.54 to 0.74).

Conclusions Early use of aspirin after coronary bypass surgery is safe and is associated with a reduced risk of death and ischemic complications involving the heart, brain, kidneys, and gastrointestinal tract. (N Engl J Med 2002;347:1309-17.)

Copyright © 2002 Massachusetts Medical Society.

FIRST performed nearly four decades ago, surgical revascularization of the coronary arteries is now performed in nearly 1 million patients annually — and its growth is likely to accelerate, given the aging of the world population and the increasing availability of this therapy in India and China.¹⁻³ Although there have been substantial advances in surgical technique,^{4,5} myocardial preservation,^{6,7} and hemodynamic monitoring and intensive care,⁸ complication rates continue to be troubling — especially for older and sicker patients and those in whom percutaneous interventions have failed. In fact, these high-risk patients now represent the majority of patients who undergo bypass surgery, giving rise to rates of 15 percent or higher⁸ for complications that affect not only the heart,^{9,10} but also the brain,^{11,12} the kidneys,¹³ and the intestines.^{14,15} Furthermore, these complications have largely gone unchecked, since no preventive therapy has been identified.

It is known that reperfusion of vital organs — achieved medically or by percutaneous or surgical intervention — is associated with an intense inflammatory response,^{16,17} precipitating cell and platelet activation and adherence to disrupted vascular endothelium, intravascular thrombosis, and eventually, organ ischemia and infarction.¹⁸ Consequently, therapies that facilitate the inhibition of cell activation and adhesion, attenuation of the release of complement and cytokines, and blockage of calcium entry into the cell have been sought,¹⁹⁻²¹ albeit with limited success, for patients undergoing surgical revascularization. Although antiplatelet therapy is now a mainstay of primary and secondary prevention in patients with acute and chronic cardiovascular disease,²²⁻²⁴ this therapy has not been considered for use in surgical patients, except in the

From the Ischemia Research and Education Foundation, San Francisco. Address reprint requests to Dr. Mangano at the Editorial Office, Ischemia Research and Education Foundation, 250 Executive Park Blvd., Ste. 3400, San Francisco, CA 94134, or at dtb@iref.org.

*The investigators and centers participating in this study are listed in the Appendix.

improvement of late vein-graft patency.^{25,26} Concern about bleeding has been paramount and has resulted in the preoperative discontinuation of aspirin therapy, the abrupt reversal of antithrombotic therapy,²⁷⁻³⁰ and even the active use of antifibrinolytic agents to promote clotting during the early reperfusion period.³¹ Furthermore, thrombocytopenia and platelet dysfunction are common immediately after surgical reperfusion,³²⁻³⁵ leading clinicians to surmise that any additional interference with platelet function would be ineffective, if not unsafe.^{30,32-35}

To address these issues, we conducted a prospective study to determine the incidence of fatal and nonfatal ischemic events involving the heart, brain, kidneys, and gastrointestinal tract after coronary bypass surgery and to assess the effect on these outcomes of aspirin use immediately after revascularization.

METHODS

Study Design

The Multicenter Study of Perioperative Ischemia Epidemiology II Study was prospective and longitudinal, including 5436 patients admitted with coronary artery disease that was refractory to medication who were scheduled to undergo coronary-artery bypass surgery at one of 70 medical institutions in 17 countries in North America, South America, Europe, the Middle East, and Asia. Enrollment began in November 1996 and ended in June 2000; the data base was locked on October 15, 2001. After approval had been obtained from the institutional review board at each institution and written informed consent had been obtained from the patients, 100 patients were to be prospectively enrolled at each institution according to a systematic sampling scheme: given N = the number of patients expected to undergo coronary-artery bypass grafting over a one-year period and $R = N \div 50$ (to the closest integer), every R th patient meeting the entry criteria was enrolled. If the R th patient did not meet the criteria, then the next patient scheduled for coronary-artery bypass grafting was chosen, and so on. To be eligible for enrollment, the patient had to be scheduled to undergo coronary-artery bypass grafting with the use of cardiopulmonary bypass, had to be able to complete the preoperative interview, could not be enrolled in another study or a clinical trial, and had to give written informed consent.

Study Data

For each enrolled patient, data on approximately 7500 variables were collected by independent investigators during the course of the hospitalization for coronary-artery bypass grafting (the index hospitalization), and treating physicians were blinded to the research data. Data were adjudicated centrally, with all data for each patient examined for completeness and accuracy before the data base was closed.

Measurement of Outcomes

All outcomes were prespecified, defined by the protocol, and determined by investigators who were unaware of the treatment-group assignment. Fatal and nonfatal outcomes occurring more than 48 hours after surgery and during the index hospitalization were classified as cardiac (myocardial infarction or heart failure), cerebral (stroke or encephalopathy), renal (dysfunction or failure), gastrointestinal (ischemia or infarction), or other (e.g., adverse events) complications. A diagnosis of myocardial infarction³⁶ was made if there were either new Q waves (Minnesota code 1-1-1 to 1-2-7); new persistent ST-segment or T-wave changes (Minnesota code 4-1, 4-2,

5-1, 5-2, or 9-2) and elevated values for the MB isoenzyme of creatine kinase; or evidence of acute myocardial infarction on autopsy. A diagnosis of heart failure³⁶ was made if a ventricular assist device was used; if continuous inotropic support was required for at least 24 hours; or if there was evidence of heart failure on autopsy. Cerebral outcomes¹¹ were classified as clinically diagnosed stroke or encephalopathy or evidence of a focal or global defect on computed tomography, magnetic resonance imaging, or autopsy. Renal dysfunction¹³ was defined by a serum creatinine level of at least 2.0 mg per deciliter (177 μ mol per liter), accompanied by an increase of at least 0.7 mg per deciliter (62 μ mol per liter) from base line; and renal failure was defined by either renal dysfunction and dialysis or evidence of renal failure on autopsy. Gastrointestinal ischemia¹⁵ was defined as abdominal pain most likely associated with bowel ischemia or detected on exploration; gastrointestinal infarction was defined by bowel resection or evidence of intestinal infarction on autopsy.

Clinical Care and Assessment of Aspirin Use

Clinical decisions were not controlled by the study protocol, and all patients qualifying for enrollment within the prespecified period were enrolled. Of the 5436 patients enrolled, 371 were excluded from the analysis because they withdrew from the study (32 patients), died without having undergone surgery (2 patients), cancelled or rescheduled surgery (97 patients), cancelled coronary-artery bypass grafting with cardiopulmonary bypass during that admission (132 patients), inadvertently enrolled in another study (11 patients), had incomplete data (86 patients), or had incomplete sampling, shipping, or storage of blood (11 patients). A total of 5065 patients remained in the analysis, of whom 3001 received aspirin (ranging from a total of 80 mg to a total of 650 mg) within 48 hours after revascularization. All medications — including prothrombotic and antithrombotic medications, procoagulant and anticoagulant medications, and blood products — were characterized according to day throughout the hospitalization, as well as at admission and at discharge or until death. All potential side effects associated with aspirin use, such as blood loss, gastric irritation, infection, and impaired wound healing, were recorded daily by investigators who were unaware of the treatments received.

Statistical Analysis

A chi-square test was used to compare patients who had received aspirin within 48 hours after revascularization with those who had not received aspirin in terms of the risk of death more than 48 hours after surgery. Fisher's exact test or a chi-square test, as appropriate, was used in the analysis of the risks of individual ischemic outcomes occurring more than 48 hours after surgery and involving the heart, the brain, the kidneys, or the gastrointestinal tract (secondary end points), as well as the risk of combined ischemic outcomes (composite outcome). For these analyses, odds ratios and 95 percent confidence intervals are reported, with associated P values. All predictor variables that were significant at a two-tailed nominal P value of less than 0.15 in univariate analyses were then entered into a multivariate logistic model. Stepwise logistic regression was performed, with variables retained that were significant at a two-tailed nominal P value of less than 0.05, with the use of SAS software, version 8.12 (SAS Institute).

RESULTS

Study Patients

Enrolled patients had evidence of chronic or acute cardiovascular disease, as well as risk factors for or evidence of cerebral, renal, or gastrointestinal disease (Table 1). As expected, there were small differences between the study groups. Although most cardiac med-

TABLE 1. BASE-LINE DEMOGRAPHIC AND MEDICAL CHARACTERISTICS OF THE 5022 STUDY PATIENTS WHO SURVIVED THE FIRST 48 HOURS.*

CHARACTERISTIC	ALL PATIENTS (N=5022)	PATIENTS RECEIVING ASPIRIN (N=2999)	PATIENTS NOT RECEIVING ASPIRIN (N=2023)	P VALUE
Age — yr				
Mean ±SD	64.0±9.76	63.6±9.71	64.3±9.8	<0.001
Median	64.8	64.3	65.5	<0.001
Body-surface area <1.93 m ² — no. (%)	2544 (50.9)	1415 (47.4)	1129 (56.0)	<0.001
Female sex — no. (%)	1024 (20.4)	579 (19.3)	445 (22.0)	0.02
Black race or American Indian or Hispanic ethnic group — no. (%)	401 (8.0)	221 (7.4)	180 (8.9)	0.06
Cardiac history — no. (%)				
Diabetes	1507 (30.0)	876 (29.2)	631 (31.2)	0.13
Hypertension	3374 (67.5)	1991 (66.6)	1383 (68.8)	0.10
Smoking	3475 (69.3)	2131 (71.2)	1344 (66.5)	<0.001
Hypercholesterolemia	3548 (72.5)	2182 (74.6)	1366 (69.3)	<0.001
Unstable angina	2522 (50.2)	1563 (52.1)	959 (47.4)	0.001
Myocardial infarction	2581 (52.0)	1558 (52.5)	1023 (51.1)	0.32
Congestive heart failure	1736 (34.8)	903 (30.3)	833 (41.6)	<0.001
PTCA	761 (15.2)	484 (16.2)	277 (13.7)	0.02
CABG	295 (5.9)	177 (5.9)	118 (5.8)	0.92
Medications — %				
ACE inhibitors				<0.001
At admission	40.8	38.0	44.8	
Before surgery	37.8	34.9	42.2	
Beta-blockers				<0.001
At admission	62.4	65.6	57.7	
Before surgery	64.0	68.0	58.1	
Calcium-channel blockers				<0.001
At admission	33.6	35.7	30.4	
Before surgery	31.9	33.9	29.0	
Antiplatelet therapy				<0.001
At admission	48.8	53.4	42.0	
Before surgery	23.7	26.9	19.0	
Aspirin				<0.001
At admission	46.7	52.0	38.9	
Before surgery	22.4	25.9	17.1	
Dipyridamole				
At admission	0.4	0.3	0.5	0.18
Before surgery	0.2	0.1	0.3	0.11
Other				
At admission	4.0	3.1	5.2	<0.001
Before surgery	2.4	1.8	3.2	0.001

*Data on body-surface area were missing for 12 patients who received aspirin and 8 who did not; data on diabetes were missing for 2 patients who received aspirin and 3 who did not; data on hypertension were missing for 8 patients who received aspirin and 12 who did not; data on smoking were missing for 4 patients who received aspirin and 3 who did not; data on hypercholesterolemia were missing for 75 patients who received aspirin and 53 who did not; data on myocardial infarction were missing for 33 patients who received aspirin and 21 who did not; data on congestive heart failure were missing for 18 patients who received aspirin and 18 who did not; and data on percutaneous transluminal coronary angioplasty (PTCA) were missing for 10 patients who received aspirin and 7 who did not. CABG denotes coronary-artery bypass grafting, and ACE angiotensin-converting enzyme.

ications (e.g., beta-blockers, calcium-channel blockers, and angiotensin-converting-enzyme inhibitors) continued to be administered until the time of surgery, the use of antiplatelet medications was discontinued in 50 percent of patients who had been receiving them at the time of admission to the hospital.

Adverse Outcomes

A total of 164 of the 5065 patients (3.2 percent) died during the index hospitalization, and 100 percent

of these deaths were associated with one or more adverse ischemic events. Seventy-four percent of the deaths (those of 121 patients) and 65 percent of the nonfatal ischemic events (those affecting 530 additional patients) occurred at least 48 hours after revascularization. Patients who had received aspirin within 48 hours after revascularization had a risk of dying thereafter that was one third that among patients who had not received aspirin (1.3 percent vs. 4.0 percent, $P<0.001$) (Fig. 1) and a risk of nonfatal ischemic com-

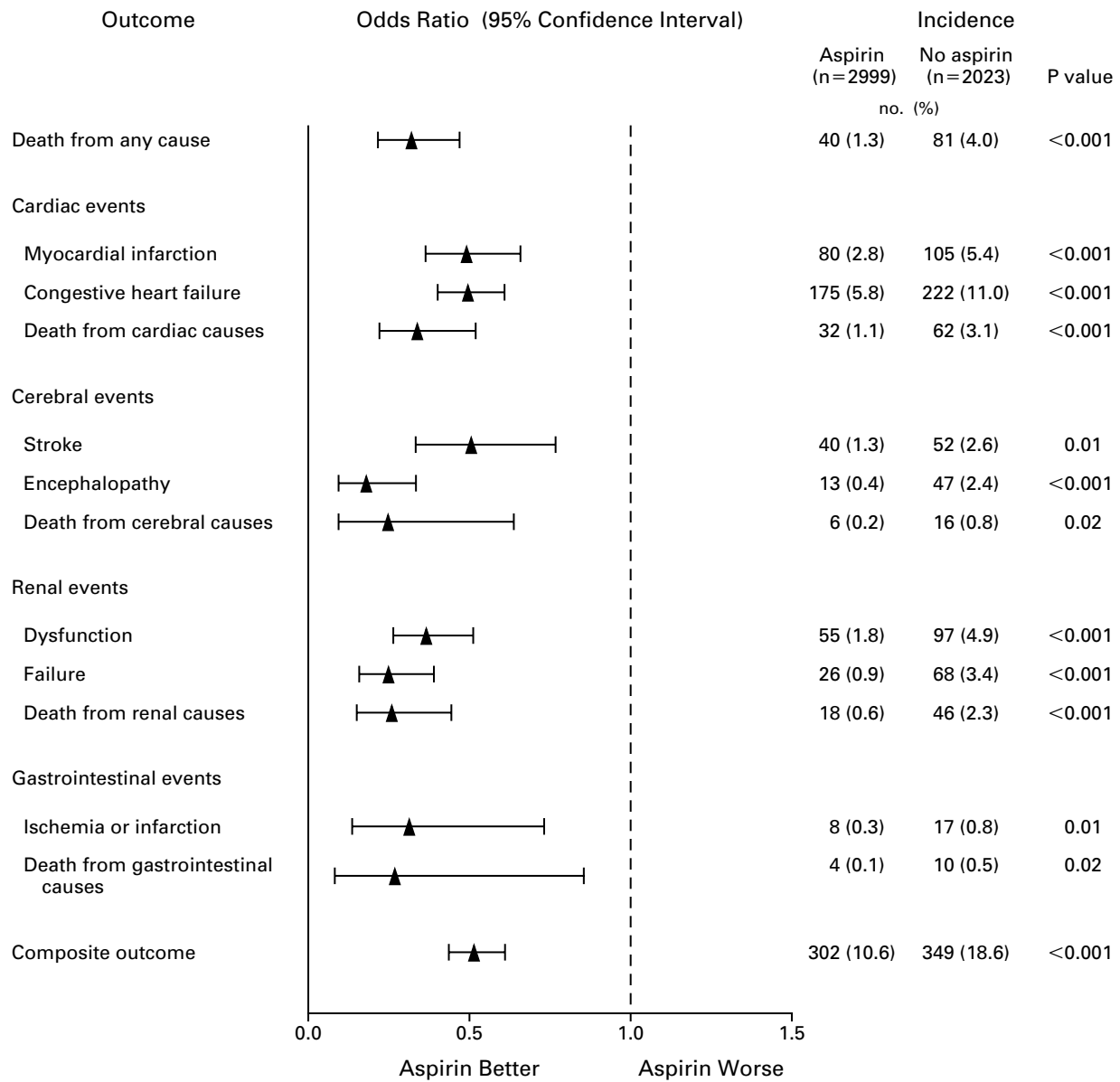
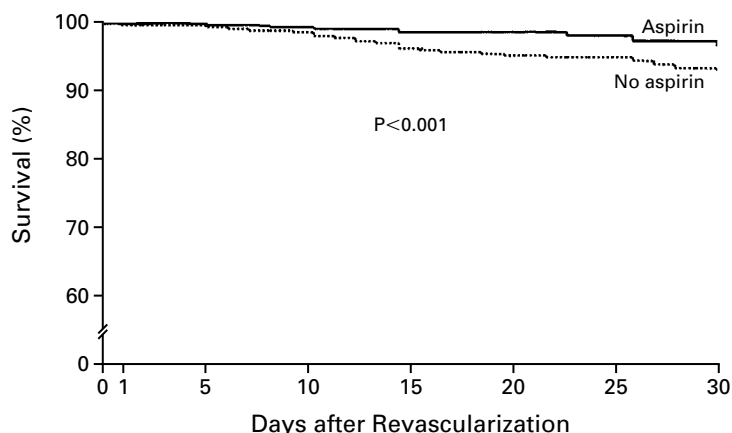


Figure 1. Fatal and Nonfatal Ischemic Outcomes among Patients Who Received Aspirin within the First 48 Hours and Patients Who Did Not.

The number of patients at risk varied with the type of outcome, since outcomes occurring within 48 hours after surgery were excluded from the analysis. A total of 73 patients had multiple causes of death.

plications involving the heart, brain, kidneys, or gastrointestinal tract that was about 60 percent of that among patients who had not received aspirin (9.4 percent vs. 15.4 percent, $P < 0.001$). The reduction in the combined rate of fatal and nonfatal outcomes was 43 percent (Fig. 1). The survival rate was higher throughout hospitalization among those who received aspirin (Fig. 2).

Within 48 hours after surgery, there were 43 deaths — in 2 of the 3001 patients who had received aspirin and 41 of the 2064 patients who had not received aspirin. However, to mitigate confounding by indication, none of these deaths were included in the analysis. Multivariate analysis demonstrated that among all potentially reversible factors, only early aspirin use was associated with improved survival during the index



CUMULATIVE DEATHS		0	13	21	28	28	29	31
Aspirin		0	13	21	28	28	29	31
No aspirin		0	18	41	58	63	64	68

Figure 2. Kaplan–Meier Analysis of In-Hospital Survival According to the Use or Nonuse of Aspirin within the First 48 Hours among the 5022 Study Patients Who Survived the First 48 Hours after Coronary-Artery Bypass Grafting.

hospitalization (Table 2). First use of aspirin after 48 hours was not associated with a significant reduction in subsequent mortality (27 percent reduction, $P=0.42$). The beneficial effect of aspirin therapy on fatal outcomes was significant in all subgroups tested, including those defined according to individual risk factors for death (such as unstable angina and previous cardiac surgery) and those defined according to other factors, such as sex, age (≥ 70 years vs. < 70 years), region (United States, Europe, Asia, Canada, South America, or the Middle East), and type of insurance (government, private, or none). No aspirin dose effect was found for either fatal or nonfatal outcomes with total doses of 75 mg, 81 mg, 100 mg, 150 mg, 162 mg, 250 mg, or 325 mg. The mean (\pm SD) length of hospital stay was 9.5 ± 7.1 days among those who received aspirin, as compared with 11.5 ± 9.4 days among those who did not receive aspirin ($P<0.001$).

The practices of discontinuing aspirin use before surgery and transfusing platelets after reperfusion, as well as the prophylactic use of antifibrinolytic agents to reduce blood loss during the perioperative period, were associated with increased risks of death and ischemic complications. Those risks were substantially reduced, but still considerable, when aspirin was used (Fig. 3). The use of aspirin was not associated with an increased frequency of adverse events (Table 3). Multivariate analysis demonstrated that the risk of hemorrhage, gastritis, infection, or impaired wound healing was not increased with aspirin use (odds ratio for these adverse events, 0.63; 95 percent confidence interval, 0.54 to 0.74).

DISCUSSION

Our findings suggest that aspirin therapy may reduce the frequency of both fatal and nonfatal outcomes associated with coronary bypass surgery. Aspirin use that was initiated during the first 48 hours after revascularization surgery was associated with a 68 percent reduction in overall mortality and similarly

TABLE 2. RESULTS OF MULTIVARIATE ANALYSES OF MORTALITY.

VARIABLE	ODDS RATIO FOR DEATH (95% CI)*	P VALUE
Aspirin use after revascularization	0.41 (0.27–0.62)	<0.001
Discontinuation of aspirin use	1.79 (1.18–2.69)	0.01
Complications after revascularization†	2.97 (1.77–4.99)	<0.001
Previous hospitalization for heart failure	2.14 (1.36–3.37)	<0.01
Creatinine >1.3 mg/dl on admission‡	2.49 (1.65–3.74)	<0.001
Heart failure on admission	2.26 (1.51–3.39)	<0.001
Warfarin or coumadin§	2.49 (1.44–4.29)	<0.01
Unstable angina	1.72 (1.15–2.58)	<0.01
Heart block on admission	1.77 (1.14–2.74)	0.01
Age >70 yr	1.62 (1.09–2.41)	0.02
Body-surface area <1.93 m ²	1.64 (1.08–2.49)	0.02
>1 Previous myocardial infarction	1.76 (1.06–2.94)	0.03

*CI denotes confidence interval.

†Complications include myocardial infarction, congestive heart failure, stroke, encephalopathy, renal dysfunction, renal dialysis, or gastrointestinal ischemia or infarction occurring within 48 hours after surgery.

‡To convert creatinine values to micromoles per liter, multiply by 88.4.

§Data are for use during the week before revascularization.

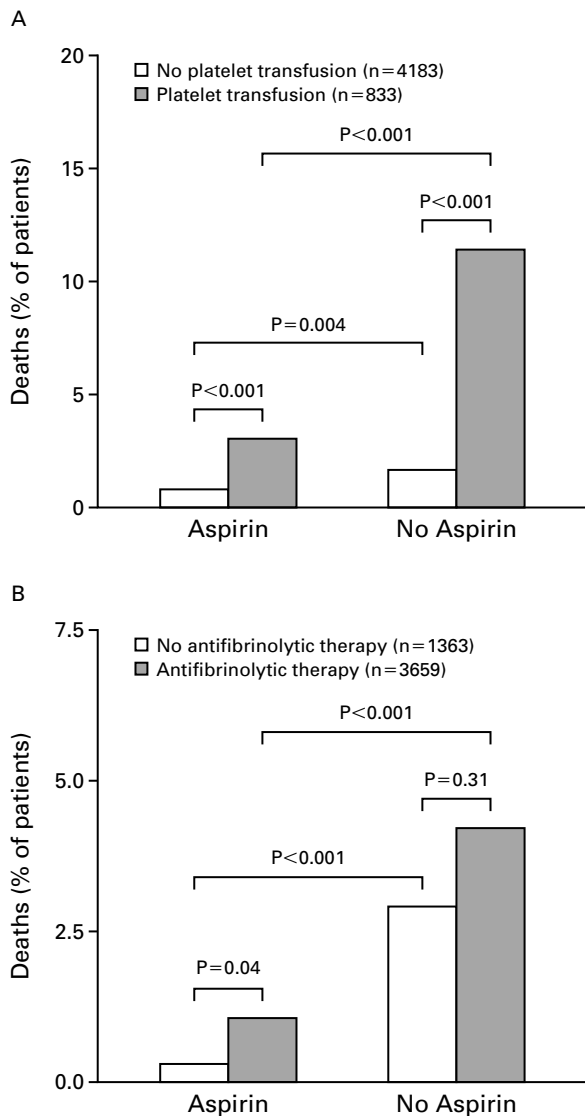


Figure 3. Mortality Associated with Platelet Transfusion (Panel A) and Antifibrinolytic Therapy (Panel B) among Patients Who Received Aspirin and Patients Who Did Not.

Antifibrinolytic therapy entailed the use of aprotinin (in 1578 patients), aminocaproic acid (in 1258 patients), tranexamic acid (in 951 patients), or desmopressin (in 61 patients). There were 189 patients who received more than one of these drugs, and 6 patients had missing data on antifibrinolytic therapy. P values for the pairwise comparisons between subgroups are shown.

substantial reductions in the rates of ischemic complications affecting the heart (44 percent reduction in fatal and nonfatal myocardial infarction or congestive heart failure), the brain (62 percent reduction in fatal and nonfatal stroke or encephalopathy), the kidneys (60 percent reduction in renal dysfunction or failure), and the intestines (70 percent reduction in ischemia or infarction). According to multivariate analy-

sis, no other factor, including any other medication, was associated with reduced rates of these outcomes after surgery. Furthermore — and contrary to current belief — aspirin therapy was safe and was not associated with an increased risk of bleeding, gastritis, infection, or impaired wound healing. Therefore, given the fact that inexpensive generic formulations are readily available, our findings support the institution of aspirin therapy during the first 48 hours after revascularization.

In patients treated medically, the effectiveness of antiplatelet therapy has been demonstrated for both primary and secondary prevention of complications of cardiovascular disease.²²⁻²⁴ Despite this evidence, however, clinicians have been reluctant to recommend early antiplatelet therapy for patients undergoing coronary bypass surgery because of two widely held beliefs — that the platelet concentration is substantially reduced during surgery because of sequestration and hemodilution³³ and that platelet function is markedly impaired during and after surgery because of hypothermia³⁷ and mechanical filtering.³²⁻³⁵ Presumably, then, the addition of antiplatelet therapy would have limited benefit and might, in fact, be unsafe.^{30,32-35} As a result, concern about excessive bleeding — and not about platelet activation and thrombosis — has dominated the thinking of those providing perioperative care, giving rise to the practices of discontinuation of aspirin therapy and the reversal of anticoagulant therapy before surgery,²⁷⁻³⁰ pervasive use of platelet transfusion during surgery,^{38,39} and even the prophylactic use of prothrombotic agents (antifibrinolytic agents) and therapies (clotting-factor transfusion) during the critical period of reperfusion.³¹ Unfortunately, few large-scale studies have attempted to determine either the efficacy or safety of these practices.

Our findings address a number of these issues and demonstrate that aspirin use in surgical patients is not associated with increased risk of hemorrhage, gastritis, infection, or impaired wound healing. Regarding efficacy, both the magnitude of the effect of aspirin and its benefit in multiple organs are noteworthy. Aspirin use was associated with a reduction of 44 to 70 percent in the frequency of major adverse events — that is, at least twice the reductions reported in studies of primary and secondary prevention.²²⁻²⁴ However, in those studies, patients were afforded primary protection by beta-adrenergic blockers, angiotensin-converting-enzyme inhibitors, and fibrinolytic agents, effectively diluting the effect of added antiplatelet therapy. Aside from beta-blockade during noncardiac surgery,⁴⁰ these therapies have never been proved effective in surgical patients. Therefore, the effects of aspirin as a single therapy are more apparent in this study.

Aspirin also had a broad effect, substantially mitigating both fatal and nonfatal damage not only to the

TABLE 3. ASPIRIN USE AND ADVERSE EVENTS IN THE 5022 STUDY PATIENTS.*

EVENT	PATIENTS RECEIVING ASPIRIN (N=2999)	PATIENTS NOT RECEIVING ASPIRIN (N=2023)	P VALUE
	no. (%)		
Hemorrhage			
Gastrointestinal tract bleeding	34 (1.1)	41 (2.0)	0.01
Other bleeding	50 (1.7)	67 (3.3)	<0.001
Return to operating room because of bleeding	57 (1.9)	105 (5.2)	<0.001
Gastritis	10 (0.3)	3 (0.1)	0.26
Infection	253 (8.4)	265 (13.1)	<0.001
Impaired wound healing	134 (4.5)	92 (4.5)	0.89

*The patients included here are those who survived the first 48 hours after revascularization.

heart, but also to the brain, kidneys, and intestines. These findings suggest that the platelet has a fundamental role in orchestrating the ischemic response to reperfusion injury by multiple organs in patients undergoing coronary bypass surgery. Three ancillary findings support this hypothesis. First, increasing the number of platelets by transfusion was associated with similar dysfunction of all four organs, and dysfunction was mitigated nearly uniformly in all four organs by aspirin therapy. Second, therapies promoting coagulation, such as transfusion of clotting factors, were associated with an increased risk of failure of these organs, which was also mitigated nearly equally in these organs by aspirin therapy. Third, medications promoting thrombosis (antifibrinolytic agents, such as aprotinin or aminocaproic acid) were associated with multiorgan failure, and aspirin therapy had similar benefit in patients who received antifibrinolytic agents and those who did not (Fig. 3B). Thus, not only do these findings support the importance of the platelet in patients undergoing coronary bypass surgery — perhaps even suggesting a common final pathway of injury to multiple diverse organs¹⁶ — but they also raise concern about practices involving the routine transfusion of platelets or clotting factors^{38,39} and the widespread use of antifibrinolytic therapy during the critical period of reperfusion in these patients.⁴¹

Our study assessed the association between the clinical use of aspirin and outcome, using prospectively defined hypotheses and methods of data collection and analysis. Although patient selection was randomized, treatment-group assignment was not, as it would be in a clinical trial. Therefore, the results may be biased by differential prescribing of aspirin (confounding by indication), with sicker patients being less likely to receive aspirin or healthier patients being more likely to receive aspirin. We addressed this possibility in several ways. First, we compared patients

who received aspirin within 48 hours after surgery with those who did not; we did not find any substantive recorded differences. Second, we excluded from analysis the 43 deaths that occurred during the first 48 hours after surgery (2 in patients who received aspirin and 41 in patients who did not) and the 291 nonfatal complications that occurred during that period (142 in patients who received aspirin and 149 in patients who did not) and assessed only those outcomes that occurred more than 48 hours after surgery. Third, in analyzing aspirin use more than 48 hours after surgery, we assessed the effect of an earlier nonfatal event on subsequent prescribing of aspirin and found only a minor effect: although subsequent aspirin use was less frequent among those with early adverse events than among those without such events (76 percent vs. 84 percent), the effect of the early use of aspirin on the risk of fatal and nonfatal events was nearly identical in these two groups (53 percent vs. 51 percent). Most important, multivariate analyses demonstrated that aspirin use within 48 hours after surgery was a significant predictor of survival after 48 hours, and its effect was independent of the occurrence or nonoccurrence of a previous nonfatal event, continuation or discontinuation of aspirin before surgery, and prescribing patterns after 48 hours. We conclude that although there may have been confounding by indication, such bias would have affected only a small proportion of patients and had no substantive effect on our findings.

The size of the effect of aspirin was unexpected: it was quite marked as compared with that reported in secondary-prevention trials (odds reductions of 15 to 47 percent).^{22,23} Unlike patients treated in secondary-prevention trials in which aspirin is added to a regimen of other proven therapies, thus diluting its effect, our patients were not offered such therapies, for none have been proved effective in patients undergoing coronary

bypass surgery. The only exception for surgical patients is perioperative beta-adrenergic blockade with atenolol, and the effectiveness of this drug has been demonstrated only in patients undergoing noncardiac surgery.⁴⁰ We recognize, however, that our findings may overestimate the effect that might be achievable in clinical practice. Finally, our findings with regard to bleeding are consistent with more recent studies addressing preoperative aspirin use^{38,39} and probably reflect the benefit of a shorter hospital stay with fewer postoperative interventions (such as catheterization and use of a ventricular assist device) in aspirin-treated patients.

Aspirin therapy, given within 48 hours after revascularization, was associated with reduced rates of death and ischemic complications involving the heart, brain, kidneys, and gastrointestinal tract. Given the safety, widespread availability, and minimal cost of aspirin therapy, our data suggest that early aspirin therapy may be considered for patients undergoing coronary bypass surgery unless its use is specifically contraindicated.

Supported by the Ischemia Research and Education Foundation.

APPENDIX

The following institutions and persons coordinated the Multicenter Study of Perioperative Ischemia Epidemiology II: *Study Chairman* — D. Mangano; *Senior Editor* — L. Savidman; *Senior Hematologist* — J. Levin; *Study Design and Analysis Center, Ischemia Research and Education Foundation* — P. Barash, C. Dietzel, A. Herskowitz, C. Ley, P. Hsu, D. Kardatzke, S. Wang, I.C. Tudor; *Editorial and Administrative Group* — D. Beatty, B. Xavier, S. Kerkela.

The following institutions and persons participated in the study: *United States*: University of Chicago, Weiss Memorial Hospital — S. Aronson; Beth Israel Hospital, Boston — M. Comunale; Massachusetts General Hospital — M. D'Ambr; University of Rochester — M. Eaton; Baystate Medical Center — R. Engelman; Baylor College of Medicine — J. Fitch; Duke Medical Center — K. Grichnik; University of Texas Health Science Center at San Antonio—Audie Murphy Veterans Affairs and University Hospital — C.B. Hantler; St. Luke's—Roosevelt Hospital — Z. Hillel; New York University Medical Center — M. Kanchuger, J. Ostrowski; Stanford University Medical Center — C.M. Mangano; Yale University School of Medicine — J. Mathew, M. Fontes, P. Barash; University of Wisconsin — M. McSweeney, R. Wolman; University of Arkansas for Medical Sciences — C.A. Napolitano; Discovery Alliance — L.A. Nesbitt; Veterans Affairs Medical Center, Milwaukee — N. Nijhawan; Texas Heart Institute, Mercy Medical Center — N. Nussmeier; University of Texas Medical School, Houston — E.G. Pivalizza; University of Arizona — S. Polson; Emory University Hospital — J. Ramsay; Kaiser Foundation Hospital — G. Roach; Thomas Jefferson University Hospital, Medical College of Pennsylvania—Hahnemann University Hospital — N. Schwann; Veterans Affairs Medical Center, Houston — S. Shenaq; Maimonides Medical Center — K. Shevde; Mt. Sinai Medical Center — L. Shore-Lesserson, D. Bronheim; University of Michigan — J. Wahr; University of Washington — B. Spiess; Veterans Affairs Medical Center, San Francisco — A. Wallace; *Austria*: University of Graz — H. Metzler; *Canada*: University of British Columbia — D. Ansley, J.P. O'Connor; Toronto Hospital — D. Cheng; Laval Hospital, Quebec — D. Côté; Health Sciences Centre—University of Manitoba — P. Duke; University of Ottawa Heart Institute — J.Y. Dupuis, M. Hynes; University of Alberta Hospital — B. Finnegan; Montreal Heart Institute — R. Martineau, P. Couture; St. Michael's Hospital, University of Toronto — D. Mazer; *Colombia*: Fundacion Clinico Shaio — J.C. Villalba, M.E. Colmenares; *France*: Centre Hospitalier Régional Universitaire Le Bocage — C. Girard; Hospital Pasteur — C. Isetta; *Germany*: Universität Würzburg — C.A. Greim, N. Roever; Universität Bonn — A. Hoefft; University of Halle — R. Loeb, J. Radke; Westfälische Wilhelms-Universität Münster — T. Mollhoff; Universität Heidelberg — J.

Motsch, E. Martin; Ludwig-Maximilians-Universität — E. Ott, P. Ueberfuhr; Universität Krankenhaus Eppendorf — J. Scholz, P. Tonner; Georg-August Universität Göttingen — H. Sonntag; *Hungary*: Orszagos Kardiologiai Intezet — A. Szekely; *India*: Escorts Heart Institute — R. Juneja; Apollo Hospital — G. Mani; *Indonesia*: National Cardiac Center — E. Siregar; *Israel*: Hadassah University Hospital — B. Drenger, Y. Gozal, E. Elami; *Italy*: San Raffaele Hospital, Università de Milano — C. Tommasino; *Mexico*: Instituto Nacional de Cardiologia — P. Luna; *the Netherlands*: University Hospital Maastricht — P. Rockaerts, S. DeLange; *Poland*: Institute of Cardiology — R. Pfitzner; *Romania*: Institute of Cardiology — D. Filipescu; *Thailand*: Siriraj Hospital — U. Prakanrattana; *United Kingdom*: Glenfield Hospital — D.J.R. Duthie; St. Thomas' Hospital — R.O. Feneck; the Cardiothoracic Centre, Liverpool — M.A. Fox; South Cleveland Hospital — J.D. Park; Southampton General Hospital — D. Smith; Manchester Royal Infirmary — A. Vohra; Papworth Hospital — A. Vuylsteke, R.D. Latimer.

REFERENCES

- Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;349:1269-76.
- Murray CJL, Lopez AD, eds. Global comparative assessments in the health sector: disease burden, expenditures and intervention packages. Geneva: World Health Organization, 1994.
- Unger F. Cardiac interventions in Europe 1997: coronary revascularization procedures and open heart surgery. *Cor Eur* 1999;7:177-89.
- Loop FD, Irarrazaval MJ, Bredee JJ, Siegel W, Taylor PC, Sheldon WC. Internal mammary artery graft for ischemic heart disease: effect of revascularization on clinical status and survival. *Am J Cardiol* 1977;39:516-22.
- Lichtenstein SV, Ashe KA, el Dalati H, Cusimano RJ, Panos A, Slutsky AS. Warm heart surgery. *J Thorac Cardiovasc Surg* 1991;101:269-74.
- Yau TM, Weisel RD, Mickle DA, et al. Alternative techniques of cardioplegia. *Circulation* 1992;86:Suppl II:II-377-II-384.
- Julia PL, Buckberg GD, Acar C, Partington MT, Sherman MP. Studies of controlled reperfusion after ischemia. XXI. Reperfusion composition: superiority of blood cardioplegia over crystalloid cardioplegia in limiting reperfusion damage — importance of endogenous oxygen free radical scavengers in red blood cells. *J Thorac Cardiovasc Surg* 1991;101:303-13.
- Mangano DT. Cardiovascular morbidity and CABG surgery — a perspective: epidemiology, costs, and potential therapeutic solutions. *J Card Surg* 1995;10:Suppl:366-8.
- Breisblatt WM, Stein KL, Wolfe CJ, et al. Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery. *J Am Coll Cardiol* 1990;15:1261-9.
- Kloner RA, Przyklenk K, Kay GL. Clinical evidence for stunned myocardium after coronary artery bypass surgery. *J Card Surg* 1994;9:Suppl:397-402.
- Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. *N Engl J Med* 1996;335:1857-63.
- Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;342:1887-92.
- Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction following myocardial revascularization: risk factors, adverse outcomes and hospital resource utilization. *Ann Intern Med* 1998;128:194-203.
- Andersen LW, Landow L, Baek L, Jansen E, Baker S. Association between gastric intramucosal pH and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor-alpha concentrations in patients undergoing cardiopulmonary bypass. *Crit Care Med* 1993;21:210-7.
- Fitzgerald T, Kim D, Karakozis S, Alam H, Provido H, Kirkpatrick J. Visceral ischemia after cardiopulmonary bypass. *Am Surg* 2000;66:623-6.
- Herskowitz A, Mangano DT. Inflammatory cascade: a final common pathway for perioperative injury? *Anesthesiology* 1996;85:957-60.
- Hennein HA, Ebba H, Rodriguez JL, et al. Relationship of the proinflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. *J Thorac Cardiovasc Surg* 1994;108:626-35.
- Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning. *Physiol Rev* 1999;79:609-34.
- Lefler DJ, Shandelya SM, Serrano CV Jr, Becker LC, Kuppusamy R, Zweier JL. Cardioprotective actions of a monoclonal antibody against CD-18 in myocardial ischemia-reperfusion injury. *Circulation* 1993;88:1779-87.
- von Asmuth EJ, Buurman WA. Endothelial cell associated platelet-activating factor (PAF), a costimulatory intermediate in TNF-alpha-induced H202 release by adherent neutrophil leukocytes. *J Immunol* 1995;154:1383-90.
- Liu Y, Sato T, O'Rourke B, Marban E. Mitochondrial ATP-dependent

- potassium channels: novel effectors of cardioprotection? *Circulation* 1998;97:2463-9.
22. Thérout P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.
23. Antiplatelet Trialists' Collaboration. 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. *BMJ* 1994;308:81-106. [Erratum, *BMJ* 1994;308:1540.]
24. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. [Erratum, *BMJ* 2002;324:141.]
25. Chesebro JH, Fuster V, Elveback LR, et al. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. *N Engl J Med* 1984;310:209-14.
26. Goldman S, Copeland J, Moritz T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration cooperative study. *Circulation* 1988;77:1324-32.
27. Taggart DP, Siddiqui A, Wheatley DJ. Low-dose preoperative aspirin therapy, postoperative blood loss, and transfusion requirements. *Ann Thorac Surg* 1990;50:424-8.
28. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *J Am Coll Cardiol* 1999;34:1262-347.
29. Pearson T, Rapaport E, Criqui M, et al. Optimal risk factor management in the patient after coronary revascularization: a statement for health care professionals from an American Heart Association Writing Group. *Circulation* 1994;90:3125-33.
30. Baumgartner WA, Owens SG, Cameron DE, Reitz BA, eds. *The Johns Hopkins manual of cardiac surgical care*. St. Louis: Mosby-Year Book, 1994.
31. Royston D, Bidstrup BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet* 1987;2:1289-91.
32. Kestin AS, Valeri CR, Khuri SF, et al. The platelet function defect of cardiopulmonary bypass. *Blood* 1993;82:107-17.
33. Khuri SF, Wolfe JA, Josa M, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss. *J Thorac Cardiovasc Surg* 1992;104:94-107.
34. Morse DS, Adams DH, Magnani B. Platelet and neutrophil activation during cardiac surgical procedures: impact of cardiopulmonary bypass. *Ann Thorac Surg* 1998;65:691-5.
35. Rinder CS, Mathew JP, Rinder HM, Bonan J, Ault KA, Smith BR. Modulation of platelet surface adhesion receptors during cardiopulmonary bypass. *Anesthesiology* 1991;75:563-70.
36. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. *N Engl J Med* 1990;323:1781-8.
37. Hessel EA II, Schmer G, Dillard DH. Platelet kinetics during deep hypothermia. *J Surg Res* 1980;28:23-34.
38. Stover EP, Siegel LC, Parks R, et al. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. *Anesthesiology* 1998;88:327-33.
39. Spiess BD, Ley C, Body SC, et al. Hematocrit value on intensive care unit entry influences the frequency of Q-wave myocardial infarction after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 1998;116:460-7.
40. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med* 1996;335:1713-20. [Erratum, *N Engl J Med* 1997;336:1039.]
41. Cosgrove DM III, Heric B, Lytle BW, et al. Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. *Ann Thorac Surg* 1992;54:1031-6.

Copyright © 2002 Massachusetts Medical Society.

CLINICAL PROBLEM-SOLVING SERIES

The *Journal* welcomes submissions of manuscripts for the Clinical Problem-Solving series. This regular feature considers the step-by-step process of clinical decision making. For more information, please see <http://www.nejm.org/hfa/articles.asp>.
