Case 1: Mr B is a 68-year-old retired steel worker who has had Canadian Cardiovascular Class III angina for the last 3 years. He has diabetes, hypertension, and hyperlipidemia, and he stopped smoking ≈5 years ago. His past medical history also includes renal insufficiency secondary to diabetic nephropathy and a mild stroke without permanent neurological deficit. Mr B had a non–ST-elevation myocardial infarction 3 months ago, and a subsequent angiogram showed severe triple-vessel coronary artery disease with preserved left ventricular function. He had been booked for coronary bypass surgery, but he was admitted to the hospital as a result of rest angina that required a nitroglycerin drip and morphine for relief. Because of his continuing rest angina while in the hospital, his cardiac surgeon decided to perform his bypass surgery on a semiurgent basis. Should Mr B continue taking his daily aspirin until the day of surgery, or should it be stopped beforehand? What does the evidence tell us about the effects of preoperative aspirin use?

The 2004 American College of Cardiology (ACC) and American Heart Association (AHA) joint guidelines for CABG surgery recommend that aspirin be started within 6 to 48 hours after surgery.1 The 2004 American College of Chest Physicians (ACCP) guideline for antithrombotic therapy in patients with saphenous vein and internal mammary artery bypass grafts recommends that it be started 6 hours after surgery.2 Both guidelines state that preoperative aspirin leads to increased postoperative bleeding; ACC/AHA guidelines recommend that aspirin be discontinued 7 to 10 days before elective surgery.

Almost all patients who present for coronary bypass surgery are undergoing chronic daily therapy with aspirin at a dose of 81 to 325 mg. This dose of aspirin improves survival in patients with ischemic heart disease.3 Aspirin has been shown to reduce the risk of vascular events (myocardial infarction, stroke, and vascular death) by 25% in patients with previous MI, by 46% in those with unstable angina, by 33% in those with stable angina, by 41% in patients with heart failure, and by 53% in those who have had previous coronary angioplasty.3 Because these are the groups of patients on whom cardiac surgeons are operating, many surgeons have these patients continue taking aspirin until the day of surgery, with the rationale that its beneficial effects for secondary prevention of acute coronary events outweigh the effects on postoperative bleeding and the transfusion requirement.4 Preoperative aspirin use may also benefit graft patency.5

Controversy continues to surround perioperative aspirin therapy; this controversy springs from the conflicting literature describing the risk/benefit ratio when aspirin is continued until the time of surgery. Aspirin may cause postoperative bleeding, which is associated with both transfusion and reexploration; these interventions are associated with increased morbidity, mortality, length of stay, and cost to the healthcare system.6 On the other hand, avoidable thrombotic events have similar consequences.

How Aspirin Works
When the German chemist Felix Hoffman first isolated acetylsalicylic acid (ASA, or aspirin) in 1897, he likely would not have predicted that it eventually would be used worldwide...
for the prevention of heart disease and acute coronary events. The antiplatelet activity of aspirin is due to its ability to irreversibly reduce thromboxane-A2 (TXA2) production. TXA2 is a potent platelet aggregator and vasoconstrictor (Figure). Because the lifespan of platelets is \( \approx 7 \) days, and ASA-induced cyclooxygenase inhibition is irreversible in the anucleate platelet, the effect of aspirin persists until platelets are replaced by the bone marrow; a measurable antiplatelet effect from a single dose of aspirin may persist for up to 1 week.

Blood flow through the cardiopulmonary bypass circuit adversely affects the number, function, and morphology of platelets. This can actually lead to platelet activation via production of TXA2. The concern is that this may lead to thromboembolic events that may compromise graft patency or cause perioperative myocardial infarction. Presumably as a result of its antiplatelet effect, aspirin improves early and late graft patency when given preoperatively and perioperatively and it improves survival after CABG when given in the perioperative setting.

### Arguments in Favor of Discontinuing Aspirin Before Coronary Bypass Surgery

The majority of studies showing increased transfusions with aspirin (Table 1) are prospective, randomized, placebo-controlled trials with sample sizes ranging between 34 and 772 patients. This is compared with the studies that suggest that aspirin does not lead to increased transfusions (Table 2); the majority of these studies are of lower methodological quality and include only 2 prospective, randomized trials, of which one was neither blinded nor placebo controlled and the other excluded a large number of patients after randomization.

There is clear evidence that starting aspirin within 48 hours after surgery improves both graft patency and survival. Whether aspirin administered preoperatively improves graft patency remains controversial; the only large, prospective, randomized, controlled trial showing improved saphenous vein graft patency with preoperative aspirin was the one by Goldman et al; however, the aspirin group in that trial may have had higher rates of graft patency because of the aspirin they received after surgery. This statement is further supported by a later prospective, randomized, controlled trial that showed no difference in graft patency when both aspirin and placebo groups received aspirin after surgery.

### Arguments in Favor of Continuing Aspirin Before Coronary Bypass Surgery

In 1991, Goldman and colleagues reported a randomized trial that failed to show any improvement in graft patency as a result of preoperative aspirin. Limitations of that study include the fact that it dates from before the age of routine internal mammary artery grafting; of the 357 patients with angiographic follow-up, only 246 had internal mammary artery grafts. In a subgroup analysis, there was evidence of a trend toward improved graft patency in patients allocated to aspirin who had internal mammary artery grafts. The effects of aspirin on the patency of radial artery, right internal mammary artery, Y, T, and skip grafts is unknown.

Although it is unclear whether the use of preoperative aspirin increases graft patency, there is reasonably suggestive evidence that it reduces mortality by as much as 45% in patients who have undergone bypass surgery. Thus, the beneficial effect of preoperative aspirin may be attributable to its ability to prevent perioperative coronary and cerebrovascular events or events that occur while the patient is awaiting surgery rather than a direct beneficial effect of the intervention on the rates of graft thrombosis.

Furthermore, the published trials that fail to support increased graft patency and those that suggest increased bleeding in patients receiving preoperative aspirin were derived from selected cohorts of patients who likely had a reduced risk of adverse outcomes compared with the average patient undergoing CABG. Of the 6 studies in Table 1, 4 included only elective

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**Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1), which prevents conversion of arachidonic acid (AA) to prostaglandin G (PGG) and H2 (PGH2), which are converted to TXA2, a potent activator of platelet aggregation.**

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**Does Preoperative Aspirin Lead to Increased Transfusions?**

Tables 1 and 2 summarize currently available studies describing the impact of preoperative aspirin use in coronary bypass patients and its effects on transfusion requirements.
CABG patients,13–16 and among these, 2 excluded females13,14 and 1 excluded patients with diabetes mellitus.15 At the same time, the Society of Thoracic Surgeons database reports that during the period between 1990 and 1999, there was a 10% decrease in elective CABG cases, an 87% increase in urgent cases, a 12% increase in female patients, and a 53% increase in diabetic patients.25

The application of recommendations derived from selected cohorts is thus problematic because patients undergoing CABG surgery are getting older, sicker, and becoming at higher risk with each passing year. They also are at higher risk of having acute coronary events, as indicated by an increased proportion of them having New York Heart Association class IV symptoms.25

The decision not to continue the use of aspirin is based on the fact that its use likely increases the risk of bleeding. Careful review of the data supporting the hypothesis that aspirin increases the risk of hemorrhage suggests that this risk may have been attributable to aspirin doses far larger than those used in current clinical practice. For example, in Table 1, 5 of the 6 studies used aspirin doses well in excess of our present usual dose of 81 mg/d.12–16

The risk of bleeding attributable to aspirin is likely reduced by other perioperative interventions; for example, antifibrinolytics such as aprotinin or

### Table 1. Studies Showing Preoperative ASA Increases Transfusion Requirements

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Description</th>
<th>ASA Dose(s)</th>
<th>Primary End Point/Analysis</th>
<th>Results/Notes</th>
<th>Antifibrinolytic Used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferraris et al (1988)12</td>
<td>Nonblinded RCT, n=34 (16 ASA, 18 placebo), Elective or urgent CABG</td>
<td>325 mg/d</td>
<td>Bleeding, transfusion</td>
<td>ASA given day before surgery</td>
<td>Yes (some patients)</td>
</tr>
<tr>
<td>Sethi et al (1990)13</td>
<td>RCT, n=772 (471 ASA daily, 3 times daily, or in combination with dipyridamole vs 301 given placebo or sulfinpyrazone), Elective CABG, Males only</td>
<td>325–975 mg/d</td>
<td>Bleeding, transfusion</td>
<td>ASA given 48h before surgery</td>
<td>No</td>
</tr>
<tr>
<td>Goldman et al (1991)14</td>
<td>RCT, n=489 (ASA or placebo), Elective CABG, Males only</td>
<td>325 mg/d</td>
<td>Graft patency</td>
<td>ASA or placebo 12 h before surgery</td>
<td>NA</td>
</tr>
<tr>
<td>Kallis et al (1994)15</td>
<td>RCT, n=100 (50 ASA, 50 placebo), Elective CABG, Diabetics excluded</td>
<td>300 mg/d</td>
<td>Bleeding, transfusion</td>
<td>ASA given for 2 weeks before surgery</td>
<td>No</td>
</tr>
<tr>
<td>Taggart et al (1990)16</td>
<td>Prospective cohort, n=202 (101 ASA, 101 control), Elective CABG</td>
<td>75–300 mg/d</td>
<td>Bleeding, transfusion</td>
<td>ASA continued to morning of surgery</td>
<td>NA</td>
</tr>
<tr>
<td>Ferraris et al (2002)17</td>
<td>Retrospective, propensity-matched study, n=2606 (1900 ASA, 706 control) CABG, combined CABG, or redo CABG</td>
<td>NA</td>
<td>Transfusion, reoperation</td>
<td>ASA within 12 h of surgery</td>
<td>NA</td>
</tr>
</tbody>
</table>

RCT indicates randomized, controlled trial.
Tranexamic acid are now used routinely and appear to reduce the overall rates of bleeding without increasing adverse outcomes.26,27 One study that administered perioperative aminocaproic acid to both the aspirin and control groups undergoing reoperative CABC showed no significant difference in bleeding.28 Special importance lies in the fact that this group traditionally has more postoperative bleeding because of increased pump times and tissue dissection.

### TABLE 2. Studies Showing Preoperative ASA Does Not Increase Transfusion Requirements

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Description</th>
<th>ASA Dose(s)</th>
<th>Primary End Point/Analysis</th>
<th>Results/Notes</th>
<th>Antifibrinolytic Used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson et al (1978)18</td>
<td>Prospective cohort, retrospective matched control</td>
<td>600–2400 mg/d</td>
<td>Bleeding, transfusion</td>
<td>ASA within 2–7 d of surgery</td>
<td>NA</td>
</tr>
<tr>
<td>Karwande et al (1987)23</td>
<td>Nonblinded, nonplacebo, RCT</td>
<td>80 mg/d</td>
<td>Bleeding, transfusion</td>
<td>ASA midnight before surgery</td>
<td>No</td>
</tr>
<tr>
<td>Ferraris et al (1989)19</td>
<td>Retrospective, case-controlled, single surgeon</td>
<td>NA</td>
<td>Excessive transfusion requirement</td>
<td>15 Patients given ASA within 7 d preoperatively</td>
<td>NA</td>
</tr>
<tr>
<td>Rawitscher et al (1991)7</td>
<td>Prospective, observational</td>
<td>85–325 mg/d</td>
<td>Bleeding, transfusion</td>
<td>ASA daily for 7 d before surgery</td>
<td>NA</td>
</tr>
<tr>
<td>Hockings et al (1993)24</td>
<td>RCT</td>
<td>100 mg/d</td>
<td>Graft patency</td>
<td>140 Patients randomized, 38 excluded after randomization because ASA or other NSAIDs prescribed for TIA or MSK symptoms</td>
<td>NA</td>
</tr>
<tr>
<td>Reich et al (1994)20</td>
<td>Retrospective cohort</td>
<td>NA</td>
<td>Bleeding, transfusion</td>
<td>ASA within 7 d of surgery</td>
<td>No</td>
</tr>
<tr>
<td>Vuylsteke et al (1997)22</td>
<td>Prospective, observational</td>
<td>≤325 mg/d</td>
<td>Bleeding, transfusion</td>
<td>ASA within 7 d of surgery</td>
<td>No</td>
</tr>
<tr>
<td>Dacey et al (2000)9</td>
<td>Retrospective, case-control</td>
<td>NA</td>
<td>Mortality</td>
<td>ASA within 7 d of surgery</td>
<td>NA</td>
</tr>
<tr>
<td>Ray et al (2003)21</td>
<td>Retrospective cohort</td>
<td>NA</td>
<td>Transfusion</td>
<td>ASA within 7 d of surgery</td>
<td>NA</td>
</tr>
</tbody>
</table>

**RCT** indicates randomized, controlled trial; **NSAID**, nonsteroidal antiinflammatory drug; **MSK**, musculoskeletal; **TIA**, transient ischemic attack.
Preoperative Aspirin and Its Role in Current Clinical Practice

The decision to discontinue aspirin 7 days before CABG surgery necessarily presupposes that the adverse consequences of bleeding exceed adverse outcomes due to thromboembolic events; however, careful analysis of the available literature suggests that this conclusion may be premature. The risk of hemorrhage probably has been overestimated (if only because of the lack of antifibrinolytic use), whereas the populations of patients studied in aspirin-discontinuation trials likely had a lower risk of thrombosis than patients currently seen in day-to-day clinical practice. Until additional good-quality evidence is available that examines the effect of preoperative aspirin on perioperative myocardial infarction, stroke, mortality, and postoperative bleeding in current CABG patients and updated perioperative surgical and anesthesia practices, it is likely that many cardiac surgeons will continue to keep their patients on aspirin therapy until the time of surgery.

Mr B’s cardiac surgeon decided to have him continue taking 81 mg of enteric-coated aspirin until the day of surgery given his unstable angina and previous stroke. Mr B received tranexamic acid perioperatively and an additional dose of protamine in the intensive care unit. He did not require any red cell transfusions. His recovery postoperatively was unremarkable, and he was discharged from the hospital 4 days after surgery.

References


23. Karwanne SV, Wexler BK, Gay WA Jr, Subramanian VA. Effect of preoperative antiplatelets drugs on vascular posta-


