Aspirin Withdrawal Prior to Invasive Medical Procedures: A Strategy Based on Thromboembolic and Bleeding Risk Stratification

Auryan Szalat MD, Gilli Erez MD and Eran Leitersdorf MD

Department of Internal Medicine B, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Key words: aspirin, thromboembolic risk, invasive procedure, low molecular weight heparin, bleeding complication

Abstract

Background: The management of aspirin therapy before an invasive procedure poses a frequent clinical dilemma due to uncertainty regarding bleeding versus thromboembolic risks associated with continuation or withdrawal of the drug. There are no evidence-based data to refer to.

Objectives: To assess the opinions of internal medicine physicians regarding aspirin therapy prior to an invasive procedure.

Methods: A questionnaire presenting nine hypothetical cases with different combinations of bleeding and thromboembolic risk was given to physicians in an internal medicine division during a personal interview. For each case the participants had to choose between withdrawal of aspirin prior to an invasive procedure, continuation of aspirin, or substitution of low molecular weight heparin for aspirin.

Results: Sixty-one physicians participated in the survey. For a patient with low thromboembolic risk, 77% (95% confidence interval 65.3–86.3%), 95% (87.2–98.7%) and 97% (89.6–99.5%) of physicians elected to discontinue aspirin prior to a low, intermediate or high bleeding risk procedure, respectively. For intermediate risk patients, 23% (95% CI 13.7–34.7%), 59% (46.4–70.8%) and 74% (61.7–83.6%) would discontinue aspirin prior to a low, intermediate or high risk procedure, and 5% (95% CI 1.3–12.8%), 23% (13.7–34.7%) and 18% (9.9–29.2%) would substitute LMWH for aspirin. For a patient with high thromboembolic risk, 1.6% (95% CI 0.08–7.8%), 11.5% (5.2–21.4%) and 18% (9.9–29.2%) recommended discontinuing aspirin prior to a low, intermediate or high risk procedure, respectively. In these situations, 18% (95% CI 9.9–29.2%), 53% (40.0–64.7%) and 57% (44.8–69.3%), respectively, would substitute LMWH for aspirin.

Conclusions: The results of the current investigation may help practicing physicians to decide whether to discontinue aspirin therapy prior to invasive procedures. The possible use of LMWH to replace aspirin as suggested here should be further evaluated in a controlled clinical study.

IMAJ 2007;9:435–438

Large-scale primary [1-5] and secondary [6-8] prevention studies have established a clear benefit for aspirin use in coronary heart disease prevention. Published clinical guidelines are accepted worldwide [9-12]. However, many interventional medical procedures require discontinuation of aspirin in order to minimize bleeding risk. A recent meta-analysis [13] suggested that the use of aspirin during invasive procedures may indeed increase the overall bleeding risk by 50%, but it does not directly influence treatment success or its related morbidity and mortality. Exceptions to this conclusion include prostatectomy, tonsillectomy and neurosurgical procedures. On the other hand, aspirin withdrawal may result in an increased risk for thrombosis. Retrospective analyses show that discontinuation of aspirin may result in a 2.3%–6% risk of thrombotic events, such as acute coronary syndrome [14-17], cerebrovascular accident [18] or lower extremity ischemia [19] within 3–12 days after cessation of the drug. The overall risk for a major cardiovascular event in patients who discontinue aspirin was recently estimated in a meta-analysis to be threefold higher than that in patients who continued aspirin use [20]. Thus, the risk related to aspirin discontinuation is not negligible, especially in CHD patients, but it cannot be adequately assessed due to the lack of controlled clinical trials. In this climate of uncertainty, physicians are faced with the difficult dilemma of aspirin continuation versus withdrawal prior to invasive procedures.

The aim of our study was to obtain the opinions of practicing physicians in an internal medicine division regarding aspirin withdrawal prior to invasive procedures, in order to create a practical tool for day-to-day decision making.

Methods

We developed a questionnaire presenting nine hypothetical cases carrying three different levels of risk for thrombosis or bleeding, in a three by three factorial design (see box). This questionnaire was delivered during a personal interview (by A.S.) to medical residents and senior physicians in the Division of Medicine at the Hadassah-Hebrew University Medical Center (Ein Kerem campus). The bleeding as well as the thrombotic risks related to the procedures were evaluated and summarized, as presented in the box. Each physician had to choose one of three management alternatives: continue aspirin, withdraw aspirin, or withdraw aspirin and start low molecular weight heparin treatment.

Statistical analysis

The primary analysis included the entire group of physicians. Results are presented as percentages with mid-*P* 95% confidence intervals calculated using the PEPI software. For each category of patients with thrombotic risk (low/intermediate/high), a pair-wise comparison was done for each clinical choice (stop aspirin/stop aspirin and start LMWH/continue aspirin) according to the bleeding risk of the procedure (low/intermediate/high) [Table 1]. The McNemar test was used for statistical analysis. The *P* values

CI = confidence interval
LMWH = low molecular weight heparin
CHD = coronary heart disease

Questionnaire delivered to internal medicine physicians during a personal interview

Nine different clinical scenarios were described to each participant. For each of the following three invasive procedures, there were three different levels of cardiovascular risk (a 3 by 3 factorial design).

The invasive procedure:

a. Low bleeding risk (directly observed and superficial): Temporal artery biopsy.
b. Intermediate bleeding risk (directly observed but deep): Colonic polyp resection.
c. High bleeding risk (blind and deep): Ultrasound-guided liver biopsy.

The cardiovascular risk:

1. Low risk patient: treated with aspirin for primary prevention of CHD (man, 55 years old, with a 10% risk to develop a coronary event in 10 years, according to the Framingham risk score).
2. Intermediate risk patient: treated with aspirin for secondary prevention of CHD (previous CVA or ST elevation myocardial infarction [STEMI] one year prior to the invasive procedure).
3. High risk patient: treated with aspirin for secondary prevention of CHD, one week after a major cardiovascular event (STEMI, treated with angioplasty and stenting).

reported are Bonferroni-corrected. A separate post hoc analysis was designed to determine differences in clinical choice based on seniority. Comparisons between the choices of senior physicians and residents were made with Fisher's exact test for 2 x 2 tables and with the chi-square test for 3 x 2 tables. The *P* values obtained for the chi-square test were exact and not the routinely reported asymptotic values.

Results

Of the 82 physicians registered in our Internal Medicine Division, 61 were recruited. These included 35 residents or fellows and 26 attending physicians with more than 8 years of professional experience. All participants answered all nine questions. The remaining 21 physicians were not available at the time the interviews were conducted. None declined to participate. The results of our survey are summarized in Table 1 and Figure 1, which also present *P* values and 95% confidence intervals.

For the low risk patient who receives aspirin for primary prevention of CHD, 77% of physicians chose to stop aspirin treatment prior to the procedure with the low bleeding risk. For moderate and high risk procedures, 95% and 97% of physicians, respectively, chose to withdraw aspirin. None chose to replace aspirin with LMWH for the low risk patient facing any bleeding risk procedure. This means that 23%, 4% and 3% would continue aspirin for a procedure with low, intermediate and high risk of bleeding, respectively.

For the patient with an intermediate thromboembolic risk, only 23% of physicians chose to discontinue aspirin before the low risk procedure. For the moderate and high risk procedures, 59% and 74% of respondents, respectively, recommended cessation of aspirin. Twenty-three percent would substitute LMWH for aspirin

Table 1. Participating physicians' clinical choices in nine hypothetical clinical scenarios

	Procedure with low bleeding risk			Procedure with intermediate bleeding risk			Procedure with high bleeding risk			Significant
Patients	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	***P* values**
Stop aspirin										
Low thrombotic risk	47	77	65.3–86.3	58	95.1	87.2–98.7	59	96.7	89.6–99.5	$\alpha = 0.01$ $\beta = 0.002$
Intermediate thrombotic risk	14	23	13.7–34.7	36	59	46.4–70.8	45	73.8	61.7–83.6	$\alpha = 0.0001$ $\beta = 0.000001$
High thrombotic risk	1	1.6	0.08–7.8	7	11.5	5.2–21.4	11	18.0	9.9–29.2	
Stop aspirin and start LMWH										
Low thrombotic risk	0	0	0–4.8	0	0	0–4.8	0	0	0–4.8	
Intermediate thrombotic risk	3	4.9	1.3–12.8	14	23	13.7–34.7	11	18	9.9–29.2	$\alpha = 0.003$ $\beta = 0.02$
High thrombotic risk	11	18	9.9–29.2	32	52.5	40.0–64.7	35	57.4	44.8–69.3	$\alpha = 0.000003$ $\beta = 0.00003$
Continue aspirin										
Low thrombotic risk	14	23	13.7–34.7	3	4.9	1.3–12.8	2	3.3	0.6–10.4	$\alpha = 0.01$ $\beta = 0.002$
Intermediate thrombotic risk	44	72.1	59.9–82.3	11	18.7	9.9–19.2	5	8.2	3.1–17.2	$\alpha = 0.0000003$ $\beta = 0.00000001$
High thrombotic risk	49	81.3	69.0–88.9	22	36.1	24.8–48.6	15	24.6	15.0–36.5	$\alpha = 0.000003$ $\beta = 0.0000003$

For each category of thrombotic risk patients, a pair-wise comparison was performed regarding clinical choice according to the bleeding risk stratum: α corresponds to the *P* value comparing this choice for a low bleeding risk procedure with the choice for an intermediate risk procedure; β corresponds to the *P* value comparing the clinical choice for a low bleeding risk procedure with the choice for a high bleeding risk procedure; and γ corresponds to the *P* value comparing the choice for an intermediate bleeding risk procedure with the one for a high bleeding risk procedure. Only statistically significant *P* values (< 0.05) appear in the tables. Note that γ was never significant. N is the number of physicians who chose any specific option presented in the table, and % represents their proportion among the 61 participants. Note that for any bleeding risk procedure, the numbers in the three sections of the table add up to 61.

CVA = cerebrovascular accident

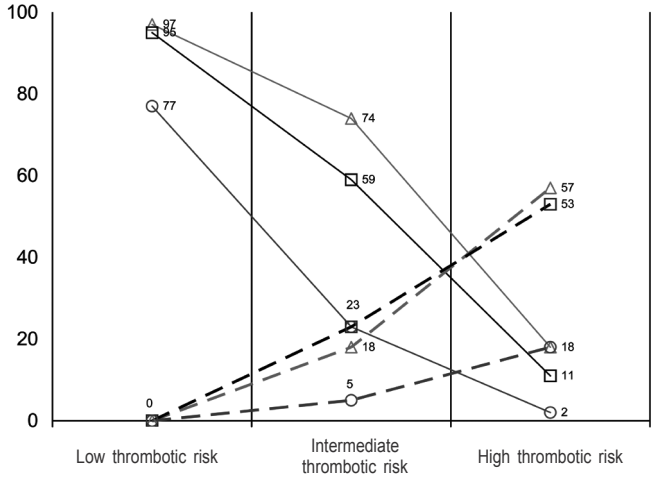

Figure 1. Percentage of physicians who elected to withdraw aspirin (solid lines) or to make a substitution of aspirin to LMWH (dashed lines) according to the bleeding risk of the procedures (○ = low, □ = intermediate, Δ = high) and the thrombotic risk of the patient.

prior to a moderate risk procedure, and 18% would offer this substitution prior to a high risk procedure. Five percent would make the substitution prior to a procedure with low bleeding risk. The decision to continue aspirin was proposed in 72%, 18% and 8% for a low, intermediate and high bleeding risk procedure, respectively.

For the patient with a high thromboembolic risk, 1.6%, 11.5% and 18% of physicians would stop aspirin prior to the procedure with the low, moderate or high bleeding risk, respectively. For the low risk procedure, 18% of physicians would recommend substitution of LMWH for aspirin. For the moderate risk procedure, this increases to 52.5%, and for the high risk procedure it reaches 57.4%. Moreover, the proportions of recommendations to continue aspirin were higher for a procedure with any bleeding risk than for patients at lower risk of thromboembolic events: 81% in low risk procedure, 36% in moderate risk procedure, 25% in high risk procedure.

For most hypothetical scenarios, there was no statistically significant difference in the responses of younger or senior physicians, the exception being in the case of the low thromboembolic risk patient scheduled for a low bleeding risk procedure. In the latter, more young physicians (who had less than 8 years of clinical experience) suggested that aspirin be discontinued than did seniors (88.9% vs. 60.0%, $P = 0.01$).

Discussion

The management of aspirin therapy prior to an invasive procedure presents a frequent clinical dilemma for which there is no available evidence-based solution. Our survey of 61 practicing internal medicine physicians may serve as a tool for decision making in common clinical situations.

In our group, most respondents recommended discontinuing aspirin in low thromboembolic risk patients prior to any procedure associated with the risk of bleeding, and to continue aspirin in high thromboembolic risk patients prior to any such procedure. For intermediate thromboembolic risk patients, most physicians suggested that aspirin be discontinued prior to high risk procedures, but continued aspirin prior to low risk ones. For the patient with intermediate risk scheduled for a moderate risk procedure, there was no general agreement.

Pair-wise comparisons showed significant statistical differences only when comparing the clinical choice for procedures with low versus intermediate or high bleeding risk [Table 1], in each cardiovascular risk stratum. Physicians' choices regarding intermediate and high bleeding risk procedures tended to be similar among any cardiovascular risk stratum. This may reflect our small sample size.

Of note, we found in the literature that colonoscopic polyp resection might be considered a procedure safely performed without discontinuation of aspirin therapy [13,21,22]. Similarly, several studies suggest that no significant complications are associated with aspirin therapy during transbronchial biopsy [13,23,24].

Our questionnaire included an option to substitute LMWH for aspirin in any clinical scenario. This option is not supported by any previously published research, but it mirrors a common 'clinical hunch', which aspires to minimize the time with the highest risk for thromboembolic events. LMWH, although mechanistically different from the antiplatelet drug aspirin, is attractive due to its short duration of action which enables withdrawal of a single dose prior to the procedure. The relatively high proportion of physicians in our survey who chose this option (57% for a high risk patient scheduled for a high risk procedure) indicates that this is in fact a clinically plausible way of action. Moreover, since we were seeking physicians' best clinical judgment, these results strongly suggest that this question requires formal research. The idea of substituting LMWH for aspirin was also recommended as an expert opinion in a recent meta-analysis of published data regarding aspirin discontinuation and the associated cardiovascular risk [20].

Our study has several limitations. Being a small, single-center study, it might reflect less variability in clinical judgment and practice than would be expected from a larger, multicenter study of physicians who are not in daily contact with one another. We intend to widen the scope of our survey and to include other internal medicine physicians in Israel. Our small sample size also prevents a comparison between the clinical choices of interventional internists (e.g., gastroenterologists) and non-interventional internists (e.g., endocrinologists). Again, this is an issue we intend to explore in the future.

Nevertheless, based on the results of our survey, we suggest the following recommendations for the management of aspirin therapy prior to invasive procedures:

- For a patient with low thromboembolic risk – discontinue aspirin prior to any bleeding risk procedure, and resume treatment once the bleeding risk has subsided.
- For a patient with high thromboembolic risk – do not withdraw aspirin prior to any bleeding risk procedure. For intermediate and high bleeding risk procedures, consider substituting LMWH for aspirin.
- For a patient with intermediate thromboembolic risk – dis-

continue aspirin prior to a procedure with high bleeding risk and continue aspirin prior to one with low bleeding risk. For such a patient scheduled for an intermediate risk procedure – consider substituting LMWH for aspirin. These patients probably present the most challenging dilemma and should be more thoroughly evaluated.

Several critical issues require didactic assessment in prospective clinical trials in order to enable rational clinical-decision making regarding the discontinuation of aspirin prior to invasive procedures. These include, but are not restricted to, an assessment of the relative efficacy of LMWH or aspirin prior to the procedure, a definition of the best time to restart aspirin or LMWH after an invasive procedure, and the risk of aspirin withdrawal in general and in several of the most common procedures in internal medicine (e.g., transbronchial biopsy, endoscopic biopsy, polyp resection, etc.). In the meantime, the decision to withdraw or continue aspirin treatment, or to use LMWH, should be taken after careful assessment of the patient's thromboembolic risk and the bleeding risk associated with the specific procedure, and according to best clinical judgment and experience. This may also warrant a coordinated approach between the referring physicians and those who perform the procedures. A national survey designed to assess physicians' opinions as well as the feasibility of conducting a relevant prospective clinical trial is currently underway. In our opinion, national guidelines for peri-procedural aspirin withdrawal are essential.

References

1. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N *Engl J Med* 1989;321:129–35.
2. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. B*r Med J* 1988;296:313–16.
3. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. L*ancet* 1998;351:233–41.
4. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. L*ancet* 1998;351:1755–62.
5. de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. L*ancet* 2001;357:89–95.
6. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. B*r Med J* 2002;324:71–86.
7. Goldstein RE, Andrews M, Hall WJ, Moss AJ. Marked reduction in long-term cardiac deaths with aspirin after a coronary event. Multicenter Myocardial Ischemia Research Group. J A*m Coll Cardiol* 1996;28:326–30.
8. Harpaz D, Gottlieb S, Graff E, Boyko V, Kishon Y, Behar S. Effects of aspirin treatment on survival in non-insulin-dependent diabetic patients with coronary artery disease. Israeli Bezafibrate Infarction Prevention Study Group. A*m J Med* 1998;105:494–9.
9. US Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. A*nn Intern Med* 2002;136:157–60.
10. Pearson TA, Blair SN, Daniels SR, et al Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. C*irculation* 2002;106:388–91.
11. Colwell JA, for the American Diabetes Association. Aspirin therapy in diabetes. D*iabetes Care* 2004;27(Suppl 1):S72–3.
12. Cairns JA, Theroux P, Lewis HD Jr, Ezekowitz M, Meade TW. Antithrombotic agents in coronary artery disease. C*hest* 2001;119(1 Suppl):228–52S.
13. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention – cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation – review and meta-analysis. J I*ntern Med* 2005;257:399–414.
14. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J A*m Coll Cardiol* 2005;45:456–9.
15. Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. C*irculation* 2004;110:2361–7.
16. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. L*ancet* 2004;364:1519–21.
17. Collet JP, Himbet F, Steg PG. Myocardial infarction after aspirin cessation in stable coronary artery disease patients. I*nt J Cardiol* 2002;76:257–8.
18. Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. N*eurology* 2004;62:1187–9.
19. Albaladejo P, Geeraerts T, Francis F, Castier Y, Leseche G, Marty J. Aspirin withdrawal and acute lower limb ischemia. A*nesth Analg* 2004;99:440–3.
20. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease. E*ur Heart J* 2006;27:2667–74.
21. Hui AJ, Wong RM, Ching JY, Hung LC, Chung SC, Sung JJ. Risk of colonoscopic polypectomy bleeding with anticoagulants and antiplatelet agents: analysis of 1657 cases. G*astrointest Endosc* 2004;59:44–8.
22. Eisen GM, Baron TH, Dominitz JA, et al., for the American Society for Gastrointestinal Endoscopy. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. G*astrointest Endosc* 2002;55:775–9.
23. Herth FJ, Becker HD, Ernst A. Aspirin does not increase bleeding complications after transbronchial biopsy. C*hest* 2002;122:1461–4.
24. Diette GB, Wiener CM, White P Jr. The higher risk of bleeding in lung transplant recipients from bronchoscopy is independent of traditional bleeding risks: results of a prospective cohort study. C*hest* 1999;115:397–402.

Correspondence: Dr. A. Szalat, Dept. of Internal Medicine B, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel.
Phone: (972-2) 677-6480/78599,
Fax: (972-2) 641-1136
email: auryan@md.huji.ac.il