

Evidence-based guideline: Periprocedural management of antithrombotic medications in patients with ischemic cerebrovascular disease

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Melissa J. Armstrong, MD¹; Gary Gronseth, MD, FAAN²; David C. Anderson, MD, FAAN, FAHA³; José Biller, MD, FACP, FAAN, FAHA⁴; Brett Cucchiara, MD⁵; Rima Dafer, MD, MPH, FAHA⁶; Larry B. Goldstein, MD, FAAN, FAHA⁷; Michael Schneck, MD, FAHA, FAAN, FACP⁸; Steven R. Messé, MD, FAAN⁹

- (1) Department of Neurology, University of Maryland School of Medicine, Baltimore, MD
- (2) Department of Neurology, Kansas University Medical Center, Kansas City, KS
- (3) Department of Neurology, University of Minnesota, Hennepin County Medical Center, Minneapolis, MN
- (4) Departments of Neurology and Neurological Surgery, Loyola University Chicago, Stritch School of Medicine, Chicago, IL
- (5) Department of Neurology, Non-invasive Neurovascular Laboratory, Hospital of the University of Pennsylvania, Philadelphia, PA
- (6) Department of Neurology, North Shore University HealthSystem, Glenview, IL
- (7) Duke Stroke Center, Duke University, Durham, NC
- (8) Departments of Neurology and Neurological Surgery, Loyola Medicine, Maywood, IL
- (9) Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA

Address correspondence and reprint requests to:
American Academy of Neurology
guidelines@aan.com

Approved by the Guideline Development Subcommittee on July 14, 2012; by the Practice Committee on August 3, 2012; and by the AAN Board of Directors on January 17, 2013.

Endorsed by the American Osteopathic Association, the European Federation of Neurological Sciences, and the European Neurological Society.

STUDY FUNDING

This guideline was developed with financial support from the American Academy of Neurology. None of the authors received reimbursement, honoraria, or stipends for their participation in development of this guideline.

DISCLOSURES

M.J. Armstrong, G. Gronseth, D.C. Anderson, J. Biller, B. Cucchiara, R. Dafer, and L.B. Goldstein report no relevant disclosures.

M.J. Schneck has participated in the past 2 years as a local principal investigator for multicenter trials sponsored by the National Institutes of Health (NIH), Lundbeck Pharmaceuticals, Brigham & Women's/Schering Plough (*Thrombolysis in Myocardial Infarction* consortium), Gore Inc, and NMT Medical. He is currently working on an investigator-initiated project to be supported by Baxter, Inc. He has served on speakers' bureaus for Boehringer-Ingelheim and Bristol-Myers-Sanofi (none in past 2 years); has received an honorarium from the American Academy of Neurology *Continuum* project, from UpToDate.com, and from various continuing medical education lectures; and has participated in expert testimony for medical malpractice cases. He has no significant stock or other financial conflicts of interest.

S. Messé has received royalties for articles on antithrombotics and stroke published on www.UpToDate.com. He has also received research support from the NIH for a study of the pharmacogenomics of warfarin and a study to evaluate neurologic outcomes from surgery.

ABSTRACT

Objective: To assess evidence regarding periprocedural management of antithrombotic drugs in patients with ischemic cerebrovascular disease.

Methods: A structured literature review identified relevant articles published through August 2011. Articles were classified according to a four-tiered evidence-rating scheme for prognostic studies, and recommendations were derived on the basis of the evidence level.

Results and recommendations: It is axiomatic that clinicians managing antithrombotic medications periprocedurally routinely weigh bleeding risks from drug continuation against thromboembolic risks from discontinuation in each patient. Neurologists should counsel that temporarily discontinuing aspirin is probably associated with increased stroke risk (Level B). Neurologists should counsel that periprocedural thromboembolic risks associated with different strategies for patients receiving chronic anticoagulation (AC) are unknown (Level U) but is probably higher if AC is stopped for ≥ 7 days (Level B).

Given minimal clinically important bleeding risks, stroke patients undergoing dental procedures should routinely continue aspirin (Level A). Stroke patients undergoing invasive ocular anesthesia, cataract surgery, dermatologic procedures, transrectal ultrasound-guided prostate biopsy, spinal/epidural procedures, and carpal tunnel surgery should probably continue aspirin (Level B). Given weaker data supporting minimal clinically important bleeding risks with vitreoretinal surgery, electromyography, transbronchial lung biopsy, colonoscopic polypectomy, upper endoscopy and biopsy, sphincterotomy, and abdominal ultrasound-guided biopsies, some stroke patients undergoing these procedures should possibly continue aspirin (Level C). Studies of transurethral resection of the prostate lack the statistical precision to exclude clinically important bleeding risks with aspirin continuation (Level U). Neurologists should counsel that aspirin probably increases bleeding risks during orthopedic hip procedures (Level B).

Given minimal clinically important increased bleeding risks, stroke patients requiring warfarin therapy should routinely continue warfarin when undergoing dental procedures (Level A) and should probably continue warfarin for dermatologic procedures (Level B). Warfarin should possibly be continued in patients undergoing electromyography, prostate procedures, inguinal herniorrhaphy, and endothermal ablation of the great saphenous vein (Level C). Whereas neurologists should counsel that warfarin probably does not increase clinically important bleeding with ocular anesthesia (Level B), studies of other ophthalmologic procedures lack the statistical precision to exclude clinically important bleeding risks of warfarin continuation (Level U). Neurologists should counsel that AC might increase bleeding with colonoscopic polypectomy (Level C).

There is insufficient evidence to support or refute periprocedural heparin bridging therapy to reduce thromboembolic events in patients who are chronically anticoagulated (Level U). Neurologists should counsel that bridging therapy is probably associated with increased bleeding risks with procedures as compared with AC cessation (Level B), but the risk difference as compared with continuing AC is unknown (Level U).

INTRODUCTION

Neurologists are frequently asked to recommend whether practitioners should temporarily stop anticoagulation (AC) and antiplatelet (AP) agents in patients with prior strokes or transient ischemic attacks (TIAs) undergoing invasive procedures. The balance of risks of recurrent vascular events with discontinuation of these agents versus increased periprocedural bleeding with continuation is often unclear, leading to variability in care and possibly adverse outcomes.

This guideline reviews evidence regarding periprocedural management of patients with a history of ischemic cerebrovascular disease receiving AC or AP agents. Four questions are addressed:

1. What is the thromboembolic (TE) risk of temporarily discontinuing an antithrombotic medication?
2. What are the perioperative bleeding risks of continuing antithrombotic agents?
3. If oral AC is stopped, should bridging therapy be used?
4. If an antithrombotic agent is stopped, what should be the timing of discontinuation?

DESCRIPTION OF THE ANALYTIC PROCESS

The American Academy of Neurology Guideline Development Subcommittee (see appendices e-1 and e-2 on the *Neurology*[®] Web site at www.neurology.org) convened an expert panel to develop the guideline. Literature searches of MEDLINE and EMBASE through August 2011 were performed in all languages using relevant MeSH terms, text word synonyms, and key words (for search strategy, see appendices e-3 and e-4). The searches identified 5,904 citations yielding 133 relevant articles which at least two authors rated by using American Academy of Neurology (AAN) prognostic classification criteria (appendix e-5). Studies were downgraded one level for indirectness of evidence (e.g., comparing patients continuing antithrombotic agents with nonusers rather than with patients discontinuing medication). Bleeding and TE risks were analyzed by intervention type. Recommendations were linked to evidence strength (appendix e-6).

Articles were included if they studied patients taking oral antithrombotic agents for primary or secondary cardiovascular disease or stroke prevention (including articles relating to atrial fibrillation), studied at least 20 subjects, included a comparison group, assessed risks of continuing or discontinuing an agent, and clearly described interventions and outcome measures. Both cardiac and stroke patients were included because risks overlap and many studies do not distinguish between the two groups. Case reports, review papers, and articles studying coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, pacemaker/defibrillator placement, and cerebrovascular procedures such as carotid endarterectomy were excluded because of confounding issues (e.g., procedure-related stroke) and because this guideline focuses on antithrombotic questions posed to treating neurologists. Non-English-language articles were included for which translations could be obtained.

The panel considered clinically relevant outcomes (e.g., vascular events, reoperation, transfusion) rather than surrogate markers (e.g.,

Figure e-1 GUSTO bleeding criteria

Severe or life-threatening bleeding:
Intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

Moderate bleeding: Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

Mild bleeding: Bleeding that does not meet moderate or severe criteria.

hemoglobin level). Bleeding was classified according to GUSTO criteria (figure e-1).^{e1} Moderate or severe bleeding was considered clinically important. Consideration was also given to clinically important specialty-specific outcomes, such as vision loss due to hemorrhage with ophthalmologic procedures or paralysis due to hemorrhage during spinal epidural procedures. Where possible, the risk difference (RD) – the arithmetic difference between the proportion of patients in one group experiencing the event relative to the proportion of patients in the other group – was calculated. We used 95% confidence intervals (CIs) of the RDs (calculated using Wilson’s method) as the measure of statistical precision.

Studies with the highest evidence levels for each intervention are discussed in the text. All studies are presented in the evidence table (table e-1), including Class III studies that did not inform recommendations.

ANALYSIS OF EVIDENCE

What is the thromboembolic risk of temporarily discontinuing antiplatelet agents?

Three studies addressed TE risks of temporarily discontinuing AP agents. A Class I double-blind, randomized, controlled trial (RCT) of subjects with cardiac risk factors (including history of TIA or stroke) undergoing various noncardiac surgeries, 90% of whom were receiving chronic aspirin therapy, randomized patients to receive aspirin 75 mg (n=109) or placebo (n=111) from 7 days preoperatively to 3 days postoperatively. Major adverse cardiac events (MACE, including acute myocardial infarction [MI], severe arrhythmia, cardiac arrest, or cardiovascular death) occurred in 1.8% (2/109) of aspirin users versus in 9.0% (10/111) of patients assigned to placebo ($p=0.02$, RD 7.2%, 95% CI 1.0% to 14.1%). Aspirin therapy resulted in a -7.2% RD (95% CI 1.3% to 13%) and an 80% relative risk (RR) reduction (95% CI 9.2% to 95%) for cardiovascular events within 30 days postsurgery. MACE and stroke/TIA occurred in 2.7% (3/109) of the aspirin group and in 9% (10/111) of the placebo group ($p=0.049$, RD 6.3%, 95% CI 0% to 13.3%).^{e2}

A case control study (Class II) examined the odds of aspirin discontinuation in the prior 4 weeks in 309 chronic aspirin users with recurrent acute ischemic stroke or TIA relative to 309 patients taking aspirin for secondary stroke prevention without a recent acute event. Subjects were matched for age, sex, and AP therapy. Aspirin discontinuation (preoperatively or for other indications) was identified in 13 (4.2%) patients hospitalized for acute stroke and in 4 (1.3%) controls. After multivariable adjustment, aspirin cessation was associated with a greater than threefold increased risk (odds ratio [OR] 3.4, 95% CI 1.08 to 10.63) for ischemic stroke or TIA. In patients with recurrent cerebral infarction, aspirin was stopped a mean of 9.5 (\pm 7) days prior to the recurrent event.^{e3}

A retrospective cohort study (Class II) using a primary care database found that 39,512 patients receiving aspirin (75–300 mg/day) for secondary cerebrovascular or cardiovascular prevention had a 40% increased risk of stroke within 1–150 days of aspirin discontinuation (RR 1.40, 95% CI 1.03 to 1.92). Stroke risk was higher within 1–15 days after the last dose, with an RR of 1.97 (95% CI 1.24 to 3.12). Absolute risk was not reported.^{e4}

Conclusion. Aspirin discontinuation is probably associated with increased stroke or TIA risk (one Class I study, two Class II studies). Estimated stroke risk varies with the duration of aspirin

discontinuation: RR was 1.97 for 2 weeks, OR was 3.4 for 4 weeks, and RR was 1.40 for 5 months (one Class II study each).

What is the thromboembolic risk of temporarily discontinuing anticoagulation?

Studies of AC discontinuation typically enroll subjects with various AC indications, each with different TE risks. Atrial fibrillation (AF) is the most common indication for chronic AC, with an annual absolute stroke risk that varies greatly depending on individual patient characteristics. Proration of the annual risk for a shorter time period cannot be used to estimate the risk of discontinuing AC periprocedurally, however, given the possible rebound effects and perioperative TE risks that are not captured in natural history cohorts.

Four Class I studies examined TE risks with warfarin discontinuation in patients receiving AC for various indications. A study of patients with chronic AC “for which oral anticoagulation [was] usually interrupted” periprocedurally reported 15 nonvenous TE events associated with 603 interventions (2.5%). As compared with that of patients with an international normalized ratio (INR) <2, the adjusted OR of nonvenous TE was 0.7 (95% CI 0.2 to 2.9) for patients with INR 2–3 and 0.3 (95% CI 0.0 to 2.5) for patients with INR >3.⁵ When subjects with an INR <2 were compared with those with an INR ≥2, the unadjusted OR was 0.65 (95% CI 0.21 to 1.97) for those patients with an INR ≥2.^{e5}

A cohort study of patients with nonvalvular AF with periprocedural warfarin interruption compared TE risk in patients with heparin bridging with risk in patients without heparin bridging. When discontinued, warfarin was held 5.3±3.0 days preoperatively, and total therapy interruption was 6.6±4.6 days. Three TE events occurred in both the bridged (n=204) and nonbridged (n=182) groups (RD with heparin bridging -2.0% [95% CI -3.4% to 2.8%]).^{e1,e6} In another cohort study, 492 subjects receiving AC for a variety of indications either stopped the AC preoperatively, received prophylactic heparin bridging, or received full-dose heparin bridging. Types of surgery were varied but mostly minor. Four TE events occurred in the group combining patients managed without bridging or with prophylactic bridging doses; this was nonsignificant (TE RD for heparin bridging -1.3%, 95% CI -3.4% to 0.8%).^{e7} A cohort study of 1024 individuals undergoing 1293 episodes of periprocedural warfarin interruption—8.3% of whom received low-molecular-weight heparin (LMWH) bridging—reported 7 patients (0.7%) with TE during 30-day follow-up, none of whom received LMWH (RD for TE in patients who were nonbridged vs. patients who were bridged 0.7%, 95% CI -3.5% to 1.5%). Patients were prescribed warfarin for numerous indications, including AF, venous TE, prosthetic valves, stroke, and left-ventricular dysfunction. Withholding warfarin for ≥7 days resulted in 5.5 times higher risk of TE events (95% CI 1.2 to 24.2) as compared with interruption for ≤5 days (absolute TE risk 2.2% vs. 0.4%).^{e8}

A Class II study of 47 patients receiving warfarin (median treatment duration 4 months, with or without concomitant dipyridamole) as secondary prophylaxis after MI reported nine (19%) TE complications within 4 weeks of warfarin discontinuation. Four (8.5%) complications were unstable angina or claudication. The other five (10.6%) complications were reinfarctions in three patients, one stroke, and one peripheral arterial thromboembolism. The RR for TE in abrupt vs. gradual discontinuation was 3.08 (95% CI 0.71 to 13.31). Laboratory assays performed in a subset of participants suggested a transient hypercoagulable state.^{e9}

Conclusion. No studies meeting inclusion criteria compared TE risks in subjects continuing warfarin with those discontinuing warfarin (with or without periprocedural heparin bridging). Studies lacked the statistical precision needed for conclusions to be drawn (one Class I study, three Class II studies with various methodologies). The TE event risk of warfarin discontinuation is probably higher if AC is stopped for ≥ 7 days (one Class I study).

What are the perioperative bleeding risks of continuing antiplatelet agents?

Dental procedures: Four studies (Class I or II) evaluated AP use during dental procedures. In a nonrandomized Class I study, local hemostasis was obtained in all 32 aspirin users (75–150 mg daily) and in 25 subjects who stopped their aspirin (timing unspecified) before dental extraction (RD 0, 95% CI -13.3% to 10.7%).^{e10} A 39-subject RCT (Class I) comparing continuation of aspirin 100 mg daily with discontinuation one week pre-dental extraction found no clinically important bleeding with continued aspirin use (RD 0, 95% CI -16.1% to 16.8%).^{e2,e11}

A prospective cohort study (Class II) comparing 27 AP users (13 on aspirin, 2 on clopidogrel, and 12 on nonsteroidal anti-inflammatory drugs [NSAIDs]) to 23 nonusers undergoing minor oral surgery found no difference in clinically important bleeding between AP users and nonusers (RD 0, 95% CI -14.3% to 12.5%) or aspirin users and nonusers (RD 0, -14.3% to 22.8%).^{e12} The pooled RD for aspirin in the two Class I studies and one Class II study was 0 (95% CI -8.3% to 8.3%).

A retrospective cohort study (Class II) compared 43 patients receiving clopidogrel or dual AP therapy (usually clopidogrel and aspirin) who were undergoing invasive dental procedures (extractions, periodontal surgery, subgingival scaling, and root planing) and found no bleeding complications (RD for dual- vs. single-agent therapy 0, 95% CI -21.5% to 11.7%).^{e13}

Conclusion. It is highly probable that aspirin does not increase minor bleeding in patients undergoing dental surgery (two Class I studies, one Class II study). However, the studies' degree of statistical precision fails to exclude an increased bleeding risk of up to 8.3%. It is possible that dual AP therapy has no increased bleeding risk over clopidogrel therapy alone (one Class II study); no bleeding events occurred in either group, but a bleeding risk of up to 11.7% cannot be excluded.

Ophthalmologic procedures: Three studies evaluated aspirin use in cataract surgeries. A cataract surgery RCT (Class I) randomized 61 patients to continue aspirin (100–500 mg daily) or discontinue it for either 2–5 days or 7–10 days. Only minor bleeding events occurred, and there were no clinically important differences in bleeding outcomes between those who continued aspirin and those who stopped aspirin (RD 0, 95% CI -8.8% to 15.5%).^{e14} A cataract cohort study (Class II) compared 24 AP users (aspirin in 88%) with 36 nonusers. Whereas subconjunctival hemorrhage was more common in the AP group (46% vs. 8.3%, $p=0.001$), only one potentially serious bleeding complication occurred in each group (RD 1.3%, 95% CI -10.3% to 17%), and both events resolved spontaneously without sequelae.^{e15} The combined RD for the Class I and Class II studies was 0.47% (95% CI -6.5% to 7.5%).

In a Class III audit of AP use during cataract procedures, there was no difference in minor (RD 0%, 95% CI -0.1% to 0.1%) or sight-threatening (RD 0%, 95% CI 0% to 0%) bleeding complications between 13110 aspirin users and 31901 nonuser controls.^{e3,e16} No adjustments were made for baseline differences, and the database did not capture whether AP therapy was continued or stopped. Whereas the risk of any complication was increased in clopidogrel users, there was no increased risk of bleeding complications in 13095 clopidogrel users versus the same nonuser controls (minor bleeding RD 0.3%, 95% CI 0% to 1.1%, sight-threatening bleeding RD 0%, 0% to 0.5%).^{e16}

Four studies included data on subjects undergoing different types of ocular anesthesia prior to other eye procedures. A cohort study of subjects undergoing retrobulbar/peribulbar block (Class II) compared 482 patients who stopped aspirin for 0–2 days or 3–14 days. The risk of any bleeding was not significantly increased in patients stopping aspirin for 0–2 days preprocedure (RD 1.7%, 95% CI -1.7% to 6.6%), and no clinically important bleeding occurred (RD 0, 95% CI -1.1% to 2.7%).^{e17} When 42 patients undergoing sub-Tenon’s anesthesia or peribulbar block while continuing aspirin were compared with a historical cohort of patients stopping aspirin prior to sub-Tenon’s anesthesia (Class II), the patients who continued aspirin had fewer subconjunctival hemorrhages (RD -15.9%, 95% CI -29.8% to -0.8%). Neither group experienced clinically important bleeding (RD 0%, 95% CI -6.9% to 8.4%).^{e18} In a Class III cohort study of subjects undergoing sub-Tenon’s anesthesia, subconjunctival hemorrhage was not more common in 75 patients taking aspirin 75 mg daily relative to 75 nonusers (RD 2.7%, 95% CI -10.2% to 15.4%). No sight-threatening bleeding occurred in either group (RD 0%, 95% CI -4.9% to 4.9%). When the same nonuser controls were compared with 56 clopidogrel users, subjects receiving clopidogrel had more subconjunctival hemorrhages (RD 9.9%, 95% CI -4.5% to 24.7%), but no sight-threatening bleeding occurred (RD 0%, 95% CI -4.9% to 8.8%).^{e19} In the Class III cataract audit described previously,^{e16} data were also presented for subjects undergoing sharp-needle and sub-Tenon’s cannula local anesthetic techniques. Minor bleeding was increased in clopidogrel users (RD 2.7%, 95% CI 1.2% to 4.8%) but not in aspirin users (RD 0.4%, 95% CI 0.1% to 0.8%). No clinically important bleeding occurred with either clopidogrel (RD 0%, 0% to 0.5%) or aspirin (RD 0%, 95% CI 0% to 0%).^{e16}

Three additional studies examined other ophthalmologic procedures. In a Class II study of patients undergoing glaucoma surgery (trabeculectomy with or without cataract extraction and tube shunt procedures) 247 subjects who continued various AP agents, including NSAIDs, were compared with 52 patients who discontinued these therapies (timing unspecified). There was no difference in bleeding complications between the two groups (RD -6.6%, 95% CI -18.7% to 1.2%).^{e20} In a Class III trabeculectomy study, 55 aspirin users had more hyphemas than nonuser controls (RD 22.9%, 95% CI 9% to 36.5%), but no clinically important bleeding occurred in either group (RD 0%, 95% CI -1.2% to 6.5%).^{e21} In a comparison of 69 patients who continued aspirin or clopidogrel for vitreoretinal surgery with 145 patients who discontinued these agents (one Class II study), patients continuing AP agents had more minor bleeding (RD 7.7%, 95% CI -1.5% to 19%) but not more clinically important bleeding (RD 0%, -2.6% to 5.3%).^{e22}

Conclusion. In three cataract studies (one Class I, one Class II, and one Class III), aspirin did not increase clinically important bleeding. However, the degree of statistical precision in the less-biased Class I and Class II cataract studies failed to exclude an increased bleeding risk of up to

7.5%. One Class III cataract study found no increase in clinically important bleeding with clopidogrel use. In two Class II and two Class III studies of ocular anesthesia, aspirin did not increase clinically important bleeding. In two studies (one Class II, one Class III) of procedures for glaucoma, aspirin use did not increase clinically important bleeding. A single Class II study of vitreoretinal surgery found no increase in clinically important bleeding in patients continuing aspirin or clopidogrel.

Dermatologic procedures: Six Class II cohort studies evaluated perioperative aspirin use during dermatologic procedures. A single study compared aspirin/NSAID continuation with discontinuation in 526 subjects and found no significant differences in study-defined severe dermatologic complications (potential significant threats to the wound or patient included severe hemorrhage, large wound bleeding lasting longer than 1 hour not stopped with pressure, acute hematoma, necrosis of skin flap, or >2-mm dehiscence) (RD -3.6% [95% CI -9.3% to 2.6%] for Mohs surgery and 2.5% [-2.8% to 6.3%] for excisional procedures).^{e23} Five studies compared outcomes for aspirin users with those for nonusers. Aspirin use was not significantly associated with increased clinically important bleeding complications in any study,^{e24-e28} with varying degrees of RD precision: -0.4% (95% CI -6.6% to 9.4%),^{e24} 0.8% (-1.6% to 6.2%),^{e4,e25} 0 (-8.0% to 9.4%),^{e26} and 6.1% (-1.9% to 19.6%).^{e27} One 253-subject study found increased suture ligation use for hemostasis in aspirin users, without differences in patient outcomes.^{e27} Another study showed a small but significant increase in any bleeding in 334 aspirin users versus 1982 nonusers (RD 1.5%, 95% CI 0.1% to 3.9%) but did not make distinctions among degrees of event severity.^{e28} Pooling the results of studies that separated mild from clinically important bleeding showed no significant increase in bleeding risk with aspirin continuation (pooled RD 0.68%, 95% CI -1.15% to 2.51%).

Conclusion. Aspirin probably does not increase clinically important bleeding with dermatologic procedures (six Class II studies).

Electromyography: One Class II cohort study examined subjects undergoing routine lower-extremity electromyography (EMG) including needle examination of the tibialis anterior muscle.^{e29} In a comparison of 57 subjects receiving AP therapy with aspirin (81 to 975 mg daily) or clopidogrel (or a combination of the two) with 51 controls, one subject in the AP group had an asymptomatic hematoma detected by ultrasonography (RD 1.8%, 95% CI -5.4% to 9.3%). No subject experienced clinically important bleeding (RD 0, 95% CI -7.0% to 6.3%).^{e29}

Conclusion. AP therapy (aspirin or clopidogrel, or both) might not increase clinically important bleeding with EMG (one Class II study).

Endoscopic procedures: Two Class II cohort studies examined AP use prior to transbronchial lung biopsy. One study found no bleeding differences between 285 aspirin users and 932 nonusers for GUSTO moderate to severe bleeding (RD 0.95% CI -0.4% to 1.3%) or study-defined serious bleeding (use of a temporary bronchus-blocker or fibrin sealant, RD 0.95% CI -1.0% to 1.8%).^{e30} When 18 clopidogrel users were compared with 574 nonusers, no moderate to severe GUSTO bleeding events were identified (RD 0, 95% CI -0.7% to 17.6%), but clopidogrel users had a higher risk of severe bleeding (as defined above) relative to nonusers (RD 27.4%,

95% CI 12.1% to 50.5%). All 12 patients receiving combination clopidogrel and aspirin also had study-defined moderate (6/12) or severe (6/12) bleeding.^{e31}

Conclusion: Continued aspirin use might not increase clinically important bleeding during transbronchial lung biopsy (one Class II study). Although clopidogrel might increase use of procedural strategies to control bleeding during transbronchial lung biopsy, one study (Class II) lacked the statistical precision to support or exclude increased clinically important bleeding with clopidogrel continuation.

Six studies examined aspirin use prior to gastrointestinal endoscopic procedures. In a cohort study (Class III) of colonoscopic polypectomy in 1657 patients, aspirin use was associated with a nonsignificant increased risk of any bleeding (severity not specified) (RD 2.0%, 95% CI -0.4% to 7.0%).^{e32} A Class II, 694-subject cohort study showed no study-defined major bleeding in aspirin or NSAID users undergoing upper endoscopy and biopsy (RD 0, 95% CI -2.7% to 4%) and no increase in study-defined major bleeding in aspirin or NSAID users undergoing colonoscopic polypectomy (RD 0, 95% CI -2.3% to 2.4%).^{e33} Pooling the results of the two polypectomy cohort studies demonstrates no significantly increased bleeding in groups taking aspirin or NSAIDs (pooled RD 0.96%, 95% CI -0.7% to 2.6%). Aspirin was not a significant risk factor for bleeding in a case control study (Class III) of 81 patients with postpolypectomy bleeding relative to 81 patients who underwent colonoscopy and polypectomy without complications (OR 1.41, 95% CI 0.68 to 3.04).^{e34} Aspirin also was not a risk factor for delayed postpolypectomy bleeding in a case control study (Class III) where 41 patients with delayed postpolypectomy bleeding were compared with 132 controls (OR 1.1, 95% CI 0.5 to 2.2).^{e35}

A sphincterotomy study (Class II) showed no increase in clinically important bleeding risk in 124 patients who continued aspirin as compared with 116 patients who stopped aspirin one week before the procedure (RD -1.0%, 95% CI -6.4% to 3.9%).^{e36} In a Class III case control study comparing 40 patients with bleeding following endoscopic sphincterotomy with 86 controls matched for age, gender, and procedure date, exposure to AP agents (primarily aspirin) was not associated with bleeding (OR 0.41, 95% CI 0.13 to 1.31).^{e37}

Conclusion. Continued aspirin use might not increase clinically important bleeding with colonoscopic polypectomy (one Class II study, three Class III studies), upper endoscopy and polypectomy (one Class II study), or sphincterotomy (one Class II study, one Class III study).

Urologic procedures: Two Class II studies examined aspirin use in patients undergoing transrectal ultrasound (TRUS)-guided prostate biopsy. In a study comparing 387 aspirin users to 731 nonusers, aspirin users self-reported more hematuria and rectal bleeding and longer bleeding duration on a questionnaire, but no clinically important bleeding occurred in either group (RD 0%, 95% CI -0.5% to 1.3%).^{e38} Likewise, a questionnaire study comparing 152 aspirin users to 282 nonusers undergoing TRUS-guided extended prostate biopsy found that aspirin users self-reported longer duration of hematuria and rectal bleeding than nonusers but no differences in bleeding rates. Clinically important bleeding did not occur in either group (RD 0%, 95% CI -1.3% to 2.5%).^{e39}

Two studies examined aspirin use with transurethral resection of the prostate (TURP). An RCT (Class I) randomizing aspirin users to continued aspirin 150 mg daily (n=26) or placebo (aspirin cessation, n=27) for 10 days preprocedure found no statistical difference in transfusion requirements ($p=0.280$, data insufficient to calculate 95% CI). The RD of readmission due to secondary hemorrhage was not significantly different between aspirin and placebo groups (6.8%, 95% CI -27.5% to 14.7%).^{e40} A cohort study (Class III) comparing 40 aspirin users with 42 nonusers found no difference in average units of transfused red blood cells (mean units 1.4 in aspirin users and 1.7 units in controls). Two aspirin users had postoperative hemorrhage requiring reoperation (RD 5.0%, 95% CI -4.1% to 16.5%).^{e41}

Conclusion. Aspirin probably does not increase clinically important bleeding with TRUS-guided prostate biopsy (two Class II studies, pooled RD 0, 95% CI -0.47% to 0.47%). In one Class I study and one Class III study, aspirin did not increase transfusion, readmission, or reoperation requirements peri-TURP. However, the studies lacked the statistical precision to exclude clinically important increased bleeding risks with aspirin continuation.

Spinal or epidural anesthesia/pain procedures: Two Class II anesthesia studies examined periprocedural aspirin and NSAID use. A cohort study found no clinically important bleeding complications (including spinal hematomas) in 193 aspirin users (median dose 350 mg daily) or nonusers (538 patients, 614 procedures) undergoing spinal or epidural anesthesia (RD 0, 95% CI -0.6% to 2%).^{e42} A study of epidural steroid injections found no clinically important bleeding complications (including spinal hematomas) in 134 aspirin users or 831 nonusers (RD 0, 95% CI -0.5% to 2.8%).^{e43} No studies examining AP use prior to lumbar punctures were identified.

Conclusions. Aspirin probably does not increase clinically important bleeding with spinal/epidural anesthesia/pain procedures (two Class II studies).

Orthopedic procedures: Four Class II studies and one Class III study evaluated aspirin use in peri-hemiarthroplasty or screw fixation (or both) for acute femoral fractures. One (Class II) found that 32 aspirin users had an increased risk of postoperative transfusion relative to 57 nonusers (RD 20.0%, 95% CI 1.2% to 38.9%).^{e44} A Class II study including 41 revision hip arthroplasties also showed that aspirin/NSAID users required more units of transfused blood (1790 ± 1344 mL) than did nonusers (954 ± 605 mL) ($p<0.05$). Other bleeding complications were not reported.^{e5,e42} Another Class II cohort study found that aspirin was associated with increased mean blood loss in 546 patients undergoing surgeries for hip fracture in both univariate ($p=0.02$) and multivariate ($p=0.02$) analyses, but clinically relevant details (e.g., transfusion rates) were not reported, and data were insufficient for RD calculations.^{e45} In contrast, a Class II study comparing 32 aspirin users to 115 nonusers with hip fracture undergoing hemiarthroplasty^{e46} found that aspirin was not associated with clinically important bleeding (RD -2.1%, 95% CI -8.3% to 10.8%) or death (RD -1.1%, 95% CI -7.2% to 12.1%). A Class III cohort study found no difference in the proportion of patients requiring a transfusion (RD 4.1%, 95% CI -13.1% to 22.3%) in a comparison of 40 aspirin users and 58 nonusers with hip fracture undergoing operative fixation with either dynamic hip screw or hemiarthroplasty.^{e47}

Two studies examined surgery in patients with hip fracture using clopidogrel. In a Class II study previously mentioned^{e6,e46} no clinically important bleeding (RD -5.5%, 95% CI -11.5% to

17.5%) or death (RD -4.5%, 95% CI -10.2% to 18.4%) occurred in subjects taking clopidogrel relative to nonusers, but the small number of clopidogrel users limited statistical precision. Surgery was typically performed in clopidogrel users 3 days after presentation and cessation of the clopidogrel.^{e46} A Class III matched cohort study compared 29 clopidogrel users and 32 nonusers undergoing nonelective orthopedic (mostly hip) surgeries.^{e48} Clopidogrel users stopped the medication on admission, but surgery was performed on average 1.88 days after presentation, and 28 of the patients had surgery within 5 days. In patients undergoing surgery within 5 days, the number of patients transfused was not different between clopidogrel users and nonusers for all nonelective orthopedic surgeries (RD 19.5%, 95% CI -6.1% to 41.7%) and when only hip fracture surgeries were considered (RD 25.1%, -2.3% to 47.6%). Thirty-day mortality was also no different between clopidogrel users and nonusers when all nonelective orthopedic surgeries (RD -3.4%, -17.2% to 8.9%) or just those procedures related to hip fractures (RD -3.7%, 95% CI -18.3% to 10.9%) were considered.^{e48} Again, however, small sample sizes limit statistical precision.

Two Class II studies examined AP use during carpal tunnel syndrome (CTS) surgery. In a retrospective cohort study in which 31 patients received AP therapy prior to surgery (30 aspirin users, 1 clopidogrel user), 6 patients continued AP therapy and 25 stopped it. There was no postoperative hemorrhage in either group (RD 0%, 95% CI -13.3% to 39.0%).^{e49} In a prospective cohort study comparing 45 aspirin users undergoing CTS surgery with 312 nonusers, one aspirin user had a minor postoperative subcutaneous hematoma (RD 2.2%, 95% CI 0% to 11.6%), but no clinically important bleeding occurred in either group (RD 0%, 95% CI -1.2% to 7.9%).^{e50} The combined RD for these two studies is 0% (95% CI -3.0% to 3.0%).

Conclusions. Whereas the results of four Class II studies and one Class III study of aspirin use and hip surgeries vary, the direction of the 95% CIs suggests that aspirin probably increases blood loss or transfusion, or both. Statistical precision was insufficient to draw conclusions regarding clopidogrel use in patients undergoing hip fracture surgery (one Class II study, one Class III study) and other nonelective orthopedic procedures (one Class III study). Aspirin probably does not result in clinically important bleeding with CTS surgery (two Class II studies).

Other procedures: Two studies evaluated patients receiving aspirin undergoing various (mostly invasive) noncardiac surgical procedures. A Class I RCT of subjects with cardiac risk factors randomized patients to receive aspirin 75 mg (n=109) or placebo (n=111) from 7 days preoperatively to 3 days postoperatively while undergoing various noncardiac surgeries. The groups did not differ as regards bleeding-related adverse events in general (RD 1%, 95% CI -1.8% to 6.4%) or when bleeding that required reoperation was considered (RD 1.8%, 95% CI -1.8% to 6.4%).^{e2} A Class II prospective cohort study found no increase in transfusion requirements in aspirin users versus nonusers (RD 9.3%, 95% CI -24.6% to 9.6%) in 52 patients undergoing emergency surgeries.^{e51}

Three studies were identified examining ultrasound-guided biopsies. In a Class II cohort study comparing bleeding complications with elective native renal biopsy at one center that continued AP agents (primarily aspirin) with another center in which AP agents were stopped for 5 days preprocedure,^{e52} aspirin users had more minor bleeding (defined as a fall in hemoglobin ≥ 1.0 g/dL that did not necessitate transfusion, RD 19%, 95% CI 5% to 31.6%) but not more clinically

important bleeding (RD 1.3%, 95% CI -4.8% to 7.2%).^{e52} In a Class III study of 232 percutaneous ultrasound-guided biopsies of pancreas transplants in 88 patients, 166 biopsies were performed while patients were taking aspirin. Clinically important bleeding complications were not more common in procedures performed during aspirin use (RD -1.9%, 95% CI -9.5% to 1.9%).^{e53} In comparisons of 3195 percutaneous liver, kidney, lung, pancreas, and other biopsies performed within 10 days of aspirin administration with 11986 biopsies in patients not receiving aspirin, rates of clinically important bleeding were not found to be increased in aspirin users (RD 0.1%, 95% CI -0.1% to 0.5%) in another Class III study.^{e7,e54}

Four additional Class II studies examining clopidogrel use during noncardiac surgeries were identified. In a retrospective cohort study, patients receiving clopidogrel or ticlopidine and undergoing surgery within 3 weeks post-stent had no increase in hemorrhages requiring transfusion, regardless of whether the medication was stopped (n=10) or continued (n=25) (RD for continuation -17.9%, 95% CI -52.8% to 16.9%).^{e55} When 20 patients who took their last clopidogrel <7 days prior to inguinal herniorrhaphy were compared with 26 patients who stopped clopidogrel for ≥7 days, more patients taking clopidogrel within 7 days required admission (RD 49.6%, 95% CI 21.3% to 68.9%), but their mean length of stay was 1.0 day. No patient had an intraoperative transfusion or other intraoperative complications or readmission or reoperation at 30 days, and none died (RD for each 0%, 95% CI -12.9% to 16.1%).^{e56} In a study of subjects undergoing various major abdominal procedures, 43 patients who took their last clopidogrel <7 days prior to surgery either had more postoperative bleeding (RD 17.1%, 95% CI 1.3% to 33.3%) or died (all-cause death) (RD 11.5%, 95% CI -1.2% to 25.7%) relative to 61 patients who stopped clopidogrel for ≥7 days but had no more reoperations at 30 days (RD 1.4%, 95% CI -7.2% to 12.4%).^{e57} In a retrospective cohort study of patients undergoing general surgery, 28 of whom took clopidogrel within 6 days and 22 of whom stopped their clopidogrel for ≥7 days, patients who took their last dose of clopidogrel within a week preoperatively had more significant bleeding after surgery requiring blood transfusion (RD 12.3%, 95% CI -9.5% to 31.6%) but no increase in operative or postoperative blood transfusion (RD 6%, 95% CI -15.3% to 26.4%) or reoperation (RD 0%, 95% CI -14.9% to 12.1%), and there was no increase in numbers of deaths (RD 0%, 95% CI -14.9% to 12.1%).^{e58} In a study of patients undergoing general thoracic surgery, 33 patients taking clopidogrel at the time of surgery (14 of whom were also taking aspirin) were compared with 132 controls.^{e59} Clopidogrel was not associated with a risk of reoperation for bleeding (RD 5.3%, 95% CI -0.2% to 18.9%) or operative mortality (RD -0.8%, 95% CI -6.1% to 11.7%). There was the suggestion that subjects undergoing a redo thoracotomy were at higher bleeding risk, but the sample size was too small for conclusions to be drawn.^{e59}

Conclusions: When studies lumping various procedures are considered, aspirin users probably have no increased risk of clinically important bleeding (one Class I study, one Class II study). How this should guide clinical practice for specific procedures is unclear. When abdominal ultrasound-guided biopsies are considered as a group, aspirin might not increase the risk of clinically important bleeding (one Class II study, two Class III studies). Variations in surgeries and methodologic approach and limited statistical precision prevent conclusions from being made regarding clopidogrel use in various invasive surgeries (four Class II studies with limited statistical precision).

What are the perioperative bleeding risks of continuing anticoagulation?

Except where noted, these studies investigated patients taking AC for a variety of indications, including valvular heart disease, mechanical heart valves, atrial fibrillation (primary and secondary prevention), secondary stroke prevention, and other prior TE disease. Known coagulopathies and thrombocytopenia were generally exclusionary criteria.

Dental procedures: Four Class I studies investigated warfarin use during oral surgeries, most commonly dental extractions. An RCT compared patients continuing warfarin (n=57, mean INR 2.5) with those stopping it 2 days prior to extraction (n=52, mean INR 1.6). No patient receiving warfarin experienced clinically important bleeding (RD 0, 95% CI -6.9% to 6.3%). Two patients in the warfarin group (3.5%, 95% CI 0.9% to 11.5%) required suturing and pressure for postoperative bleeding.^{e60} Another RCT found no clinically important bleeding in patients who continued warfarin (n=33, mean INR 2.7) or those who stopped it 2–3 days preoperatively (n=32, mean INR 1.6) (RD 0, 95% CI -10.7% to 10.4%). All bleeding was controlled with local measures.^{e61} A third RCT randomized subjects to one of four groups: warfarin continuation with suturing (n=52, mean INR 2.7) or without suturing (n=48, mean INR 2.4) and warfarin discontinuation with suturing (n=56, mean INR 1.9) or without suturing (n=48, mean INR 1.8). Whereas bleeding at postoperative day 1 was slightly higher in the groups that continued warfarin, this was nonsignificant, and there was no clinically important bleeding in either group (RD 0%, -3.6% to 3.4%).^{e62} The final study was an open-label study which randomized patients to either continue their AC (warfarin or acenocoumarol) with a target INR of 2.5 (n=65, mean INR 2.89) or reduce it with a target INR of 1.8 (n=55, mean INR 1.77). There was no significant difference between groups in either the need for supplementary local hemostasis (RD 6.3%, -5.3% to 18%) or clinically important bleeding (RD 0%, -5.5% to 5.6%).^{e63} When the three studies comparing warfarin continuation and discontinuation were considered, the pooled RD was 0 (95% CI -3.1% to 3.1%).

Conclusion. It is highly probable that warfarin does not increase clinically important bleeding risks with dental extractions (four Class I studies).

Ophthalmologic procedures: Nine studies examined AC continuation during ophthalmologic procedures. Two of the studies primarily included cataract surgeries. In a Class II ocular surgery cohort study (involving mostly cataract surgeries), no clinically important bleeding occurred in those who continued warfarin (n=9) or stopped it (n=41, stopped on average 5.5 days preoperatively and restarted on average 1.8 days postoperatively). Small sample size limited precision (RD 0, 95% CI -8.6% to 29.9%).^{e64} In a Class III audit of AC use during cataract procedures, there was no difference in minor (RD 0%, 95% CI -0.1% to 0.3%) or sight-threatening (RD 0%, 95% CI 0% to 0.2%) bleeding complications between 2372 AC users and 31901 nonuser controls.^{e16} No adjustments were made for baseline differences, and the database did not capture INR or whether the AC therapy was continued or stopped.^{e16}

Four studies examined AC use with ocular anesthesia. In a Class II cohort study, no clinically important bleeding (including sight-threatening bleeding) was reported in 76 patients undergoing retrobulbar/peribulbar block regardless of whether warfarin was continued or stopped (RD 0, 95% CI -8.6% to 24.3% for stopping 0–1 days vs. ≥ 2 days). Warfarin was most commonly discontinued 2–3 days preprocedure.^{e17} When 14 patients undergoing sub-Tenon's anesthesia or

peribulbar block while continuing oral AC were compared with a historical cohort of patients stopping oral AC and using LMWH prior to sub-Tenon's anesthesia (Class II), the patients who continued AC had fewer subconjunctival hemorrhages than those who received bridging therapy (RD -33.3%, 95% CI -54.6% to -6.4%), and neither group experienced clinically important bleeding (RD 0%, 95% CI -15.5% to 21.5%).^{e18} In a Class III cohort study of subjects undergoing sub-Tenon's anesthesia, subconjunctival hemorrhage was more common in 65 patients taking warfarin relative to 75 nonusers (RD 16.7%, 95% CI 2.0% to 30.8%), but no sight-threatening bleeding occurred in either group (RD 0%, 95% CI -4.9% to 5.6%).^{e19} In the Class III cataract audit described above,^{e16} data were also presented for subjects undergoing sharp-needle and sub-Tenon's cannula local anesthetic techniques. Minor bleeding was increased in warfarin users (RD 2.9%, 95% CI 1.8% to 4.2%), but no clinically important bleeding occurred (RD 0%, 95% CI 0% to 0.3%).^{e16}

Four additional studies examined other ophthalmologic procedures. In a Class II study of patients undergoing glaucoma surgery (trabeculectomy with or without cataract extraction and tube shunt procedures) 22 subjects who continued AC (defined as warfarin, heparin, or enoxaparin with or without concomitant AP therapies) were compared with 26 patients who discontinued oral AC 2–3 days presurgery (with or without concomitant AP therapies). There was no significant difference in bleeding complications between the two groups (RD 16.4%, 95% CI -7.4% to 39.2%).^{e20} In a Class III trabeculectomy study, all 5 warfarin users (INR 1.5–4.5) had hyphemas (RD versus 307 nonuser controls 72%, 95% CI 28.2% to 76.7%) and clinically important bleeding resulting in reoperation or trabeculectomy failure, or both, within 12 months (RD versus nonuser controls 100%, 95% CI 56.5% to 100%).^{e21}

A Class II retrospective vitreoretinal surgery cohort study compared 54 patients continuing warfarin on the basis of preoperative INR. Only four bleeding complications occurred in any group (7.0% of patients); severity was not described, but all resolved spontaneously without sequelae.^{e65} In a Class III retrospective cohort study comparing 25 warfarin users (18 of whom had stopped the warfarin for <5 days) with 588 nonuser controls undergoing vitreoretinal surgery, INR results were available for only 11 patients, with a median of 1.25. Minor bleeding (RD 17.6%, 95% CI 3.6% to 37.3%), but not clinically important bleeding (RD -0.7%, 95% CI -1.7% to 12.6%), was increased in warfarin users.^{e22}

Conclusion. One Class I study and one Class III study lacked the statistical precision or details necessary to draw conclusions regarding the bleeding risk associated with warfarin continuation during cataract surgery. For patients undergoing ocular anesthesia, warfarin probably does not increase clinically important bleeding risks (two Class II and two Class III studies). Statistical precision was insufficient to make recommendations regarding AC use during glaucoma surgeries (one Class II study, one Class III study) and vitreoretinal surgeries (one Class II study, one Class III study).

Dermatologic procedures: Five Class II studies investigated AC use with dermatologic procedures, usually Mohs or excisional surgeries. One study prospectively compared 12 warfarin users with 213 nonusers and found no clinically important bleeding with warfarin use (RD 0, 95% CI -1.8% to 24.3%), but one patient in each group required a procedure for bleeding (95% CI for warfarin 1.5% to 35.4%).^{e25} Another prospective study found no bleeding complications

in 16 warfarin users or 77 nonusers (RD 0, 95% CI -4.8% to 19.4%).^{e66} A retrospective cohort study compared warfarin continuation with discontinuation and found that, in 75 patients undergoing Mohs surgery, continuing warfarin was associated with an RR of 0.8 (0.04–18.0) for study-defined moderate to severe bleeding, with moderate complications representing serious oozing >24 h, dehiscence <2 mm, or superficial slough of the flap or graft and serious complications reflecting significant intraoperative or postoperative hemorrhage, wound bleeding >1 h despite pressure, acute hematoma, necrosis of the flap or graft, or > 2-mm dehiscence. No patient in the warfarin group had moderate to severe complications whereas two subjects for whom warfarin was withheld experienced moderate complications. For excisional surgery (n=52), the RR of moderate to severe complications was 13.00 (1.60–105.49) due to 4 complications (3 moderate, 1 severe) in the warfarin group and one in the group in which warfarin was withheld.^{e23} In a cohort study in which warfarin was continued unless the INR was >3, warfarin use (n=67 with 1982 nonuser controls) was associated with an increased bleeding risk (OR 2.9, 95% CI 1.4 to 6.3) in a logistic regression model. Severity of bleeding was not analyzed, but the probability of wound exploration for bleeding or hematoma evacuation in warfarin users was 3.0% (95% CI 0.8% to 10.2%).^{e28} Another prospective cohort study found that the five observed major complications (defined as persistent bleeding, wound hematoma, skin graft loss, or infection) occurred only in the 21 patients receiving warfarin. The RR of warfarin use as compared with nonuse (n=44) was 18.33, but the 95% CI was wide (1.06 to 318.70).^{e26} The pooled RD of clinically important bleeding in all of the studies was 1.2% (95% CI -0.12% to 2.5%), but there was significant heterogeneity among studies.

Conclusion. Five Class II studies provide conflicting data regarding the effect of warfarin on bleeding complications during dermatologic procedures. Pooled risk of these heterogeneous studies suggests that warfarin is associated with a small RD for clinically important bleeding.

Electromyography: One Class II cohort study examined subjects undergoing routine lower-extremity EMG including needle examination of the tibialis anterior muscle.^{e29} When 101 subjects receiving warfarin (INR 1.5–4.2) were compared with 51 controls, two subjects in the warfarin group were found to have had asymptomatic hematomas detected by ultrasonography (RD 2.0%, 95% CI -5.2% to 6.9%). No subject experienced clinically important bleeding (RD 0, 95% CI -7.0% to 3.7%).^{e29}

Conclusion. Warfarin might not increase clinically important bleeding with EMG (one Class II study).

Endoscopic procedures: Two Class III studies examined AC use during colonoscopic polypectomy. In a retrospective cohort study of 1657 patients, warfarin (INR 1.08–1.86) was an independent risk factor for bleeding even after adjustment for other factors (OR 13.37, 95% CI 4.10 to 43.65). Of 32 total immediate postpolypectomy bleeding cases, 31 were classified as mild, and all 32 were successfully treated endoscopically. All five patients with delayed postpolypectomy bleeding required blood transfusion, but none required surgery. The difference in severity between AC users and nonusers was not reported.^{e32} In a case control study examining 41 patients who developed hematochezia requiring medical evaluation 6 hours to 14 days after colonoscopic polypectomy (versus 132 controls), resumption of warfarin and/or heparin within one week postpolypectomy was associated with increased bleeding (OR 5.2, 95%

CI 2.2 to 12.5). No patient continued AC during the procedure. All patients with bleeding complications were admitted to the hospital; 48% required transfusion, and 95% required repeat colonoscopy. Two patients required surgery.^{e35}

Conclusion. AC might increase bleeding with colonoscopic polypectomy, some of which is clinically important (one Class III study of AC continuation, one Class III study of resumption within one week postprocedure).

Urologic procedures: Two Class III studies examined AC use with urologic procedures. In a Class III cohort study of patients undergoing TRUS-guided prostate biopsy, 49 warfarin users were compared with 731 nonuser controls. Warfarin users had less hematuria (RD -23.5%, 95% CI -36.0% to -9.0%), less hematospermia (RD -12.8%, 95% CI -18.6% to -1.4%), and an insignificant difference in rectal bleeding (RD 1.3%, 95% CI -6.4% to 13.9%). No patient had clinically important bleeding (RD for warfarin -0.5%, 95% CI -1.4% to 6.7%).^{e67} In a Class III study of polyvinylpyrrolidone (PVP), 36 warfarin users had more hematuria requiring transient bladder irrigation relative to 92 nonuser controls (RD 36.2%, 95% CI 20.2% to 52.7%), but there was no clinically important bleeding in either group (RD 0%, 95% CI -4.0% to 9.6%).^{e68}

Conclusion. Warfarin might not increase clinically important bleeding when different urologic procedures are considered together (two Class III studies), but data are insufficient to determine bleeding risks for individual procedures.

Other procedures: One Class II retrospective cohort study examined perioperative warfarin use among chronic warfarin users undergoing inguinal herniorrhaphy. The RD for clinically important bleeding when patients who continued warfarin (n=19) were compared with those who discontinued warfarin without heparin (n=54) was 0 (95% CI -6.6% to 16.8%). Those who continued warfarin had more self-limited postoperative hematomas than those who discontinued warfarin (RD 8.7%, 95% CI -2.3% to 29.6%).^{e69}

Conclusion. Based on one Class II study, continuing warfarin during inguinal herniorrhaphy might result in more self-limited hematomas but not clinically important bleeding complications.

One Class II prospective cohort study examined 88 limbs in warfarin users (with or without concomitant AP use) to 92 limbs in nonusers undergoing endothermal ablation of the great saphenous vein.^{e8,e70} Warfarin users had a higher risk of minor bleeding (RD 4.7%, 95% CI -3.0% to 13.0%) but not clinically important bleeding (RD 0%, 95% CI -4.0% to 4.2%).^{e70}

Conclusion. Based on one Class II study, continuing warfarin during endothermal ablation of the great saphenous vein might result in no increased clinically important bleeding.

If oral anticoagulation is stopped, should bridging therapy be used?

As discussed regarding TE, there is insufficient evidence to support or refute differences in TE risks between chronic AC users managed with different periprocedural strategies including heparin bridging.

With regard to bleeding risks, five relevant studies were identified. A cohort study (Class I) that followed 345 patients with AF who were undergoing 386 procedures found that the RD for clinically important bleeding for procedures managed with heparin bridging was 0.7% (95% CI -2.9% to 4.3%).^{e6} In another Class I cohort study consisting mostly of minor surgeries, 492 subjects receiving AC for various indications stopped the AC preoperatively, received prophylactic heparin bridging, or received full-dose heparin bridging. Heparin was stopped 24 hours presurgery. Full heparin bridging was associated with increased odds of clinically important bleeding (OR 4.8, 95% CI 1.6 to 14.0; RD 9.5%, 95% CI 4.8% to 15.1%).^{e7} A Class I cohort study of 1024 individuals, 88 of whom received heparin bridging, reported increased study-defined major hemorrhage (bleeding that was fatal, required hospitalization with transfusion of at least 2 units of packed red blood cells, or occurred at a critical site) (RD 4.3%, 95% CI 1.5% to 10.9%) and study-defined clinically important nonmajor hemorrhage (bleeding that led to an unplanned intervention such as reoperation or nasal packing) (RD 10.6%, 95% CI 5.5% to 18.9%) in the group receiving full heparin bridging.^{e8}

In a Class II study of 57 patients undergoing robotic-assisted radical prostatectomy, subjects in the LMWH heparin group (n=14) had an increased risk of transfusion relative to those in the group who stopped oral AC without bridging (n=43) (21.4% vs. 2.1%, $p=0.042$), but other bleeding outcomes did not differ between groups.^{e71} In a Class III study of 437 patients undergoing various gastrointestinal endoscopies, patients managed with LMWH heparin had more major hemorrhagic events relative to those who stopped oral AC (RD 3.2%, 95% CI -0.2% to 9.0%).^{e72}

Only one study compared heparin bridging with oral AC continuation. In an RCT (Class I) of 214 patients in need of simple dental extractions randomized to continue oral AC or receive LMWH bridging, no TE events occurred, and all bleeding was mild and easily controlled (RD of bridging versus continuing oral AC 0, 95% CI -3.4% to 3.5%).^{e73}

Conclusion. Whereas there is insufficient evidence to support or refute a difference in TE events when heparin bridging is used (versus discontinuation of oral AC without bridging), most studies suggest that heparin bridging is probably associated with an increased risk of periprocedural bleeding in general (two Class I studies, one Class II study, one Class III study showing increased risk, with one additional Class I study showing no substantial increased risk).

There is insufficient evidence to support or refute differences in TE risk between management strategies of *continuing* oral AC versus heparin bridging. The risk of bleeding is probably similar between LMWH bridging and AC continuation in dental procedures (one Class I study), although the clinical significance of this is unclear given the evidence for AC continuation with dental procedures described above.

If an antithrombotic agent is stopped, what should be the timing of discontinuation?

Data are insufficient to support recommendations.

CLINICAL CONTEXT

Aspirin and clopidogrel both have irreversible AP activity. Effect duration is estimated to be the time required for platelet turnover, approximately 7 days.^{e74} The duration of action of a single

dose of warfarin is estimated at 2–5 days.^{e74} Given these numbers, it is generally recommended that when these agents must be discontinued preoperatively, AP agents be stopped 7–10 days, and warfarin 5 days, preprocedure if the goal is to eliminate their effects completely.^{e75} Shorter discontinuation was considered as an option in many of the reviewed studies (i.e., allowing for partial platelet and factor recovery), but no data exist regarding when this may be considered.

In patients requiring chronic antithrombotic agents to prevent TE events, stopping the agents will necessarily increase the risk of TE events, so time off the antithrombotic agents should be minimized. Current data addressing exact TE risks of temporarily discontinuing antithrombotic therapy in patients with a history of ischemic cerebrovascular disease are limited, as are data addressing theorized rebound effects. Clearly, it is important to consider the relative morbidity of potential outcomes and not just their frequency. In the perioperative setting, TE events occur infrequently, but the associated morbidity and mortality rates are high. In contrast, most reported bleeding outcomes are mild. Decisions regarding periprocedural antithrombotic therapy depend on weighing these competing risks in the context of individual patient characteristics. For example, recurrent stroke risk may be higher in patients with recent stroke or TIA,^{e76} prior large-artery atherosclerotic stroke,^{e77,e78} AF,^{e79} or hypertension, or both AF and hypertension.^{e79} Considering patient preference is also critical. In a study comparing preferences of patients with AF with those of physicians, patients were willing to experience a mean of 17.4 excess-bleeding events with warfarin and 14.7 excess-bleeding events with aspirin to prevent a stroke.^{e80} Sample clinical scenarios for guideline application are presented in appendix 1 of the summary document.

RECOMMENDATIONS

It is axiomatic that clinicians managing antithrombotic medications periprocedurally weigh bleeding risks from drug continuation against TE risks from discontinuation at the individual patient level, although high-quality evidence on which to base this decision is often unavailable. In addition, even when evidence is insufficient to exclude a difference in bleeding or shows a small increase in clinically important bleeding with antithrombotic agents, physicians may reasonably judge that the risks and morbidity of TE events exceed those associated with bleeding.

Neurologists should counsel both patients taking aspirin for secondary stroke prevention and their physicians that aspirin discontinuation is probably associated with increased stroke and TIA risk (Level B). Estimated stroke risks vary across studies and according to duration of aspirin discontinuation. Neurologists should counsel patients taking AC for stroke prevention that the TE risks associated with different AC periprocedural management strategies (continuing oral AC or stopping it with or without bridging heparin) are unknown (Level U) but that the risk of TE complications with warfarin discontinuation is probably higher if AC is stopped for ≥ 7 days (Level B).

Patients taking aspirin should be counseled that aspirin continuation is highly unlikely to increase clinically important bleeding complications with dental procedures (Level A). Given minimal clinically important bleeding risks, it is reasonable that stroke patients undergoing dental procedures should routinely continue aspirin (Level A).

Patients taking aspirin should be counseled that aspirin continuation probably does not increase clinically important bleeding complications with invasive ocular anesthesia, cataract surgery, dermatologic procedures, TRUS-guided prostate biopsy, spinal/epidural procedures, and carpal tunnel surgery (Level B). Given minimal clinically important bleeding risks, it is reasonable that stroke patients undergoing these procedures should probably continue aspirin (Level B).

Aspirin continuation might not increase clinically important bleeding in vitreoretinal surgery, EMG, transbronchial lung biopsy, colonoscopic polypectomy, upper endoscopy with biopsy, sphincterotomy, and abdominal ultrasound-guided biopsies. Given the weaker data supporting minimal clinically important bleeding risks, it is reasonable that some stroke patients undergoing these procedures should possibly continue aspirin (Level C).

Although bleeding events were rare, TURP studies lack the statistical precision to exclude clinically important bleeding risks with aspirin continuation (Level U). Patients taking aspirin should be counseled that aspirin probably increases bleeding risks during orthopedic hip procedures (Level B).

Neurologists should counsel patients that there is insufficient evidence to make recommendations regarding appropriate periprocedural clopidogrel, ticlopidine, or aspirin/dipyridamole management in most situations (Level U). Aspirin recommendations cannot be extrapolated with certainty to other AP agents.

Patients taking warfarin should be counseled that warfarin continuation is highly unlikely to be associated with increased clinically important bleeding complications with dental procedures (Level A). Given minimal bleeding risks, stroke patients undergoing dental procedures should routinely continue warfarin (Level A).

Patients taking warfarin should be counseled that warfarin continuation is probably associated with only a small (1.2%) increased RD for bleeding during dermatologic procedures on the basis of a meta-analysis of heterogeneous and conflicting studies (Level B). Thus, patients undergoing dermatologic procedures should probably continue warfarin (Level B). Patients taking warfarin should be counseled that warfarin continuation is probably not associated with an increased risk of clinically important bleeding with ocular anesthesia (Level B). However, AC practices during ophthalmologic procedures may be driven by the postanesthesia procedure.

Warfarin might be associated with no increased clinically important bleeding with EMG, prostate procedures, inguinal herniorrhaphy, and endothermal ablation of the great saphenous vein. Thus patients undergoing these procedures should possibly continue warfarin (Level C).

Although bleeding events were rare, ophthalmologic studies (other than those regarding ocular anesthesia) lack the statistical precision to exclude clinically important bleeding risks with warfarin continuation. Thus, there is insufficient evidence to make practice recommendations regarding warfarin discontinuation in ophthalmologic procedures (Level U).

Patients taking warfarin should be counseled that warfarin continuation might increase bleeding with colonoscopic polypectomy (Level C). Thus, patients undergoing this procedure should possibly temporarily discontinue warfarin (Level C).

Neurologists should counsel patients that there is insufficient evidence to make recommendations regarding appropriate periprocedural management of non-warfarin oral AC (Level U). Warfarin recommendations cannot be extrapolated with certainty to other AC agents.

There is insufficient evidence to determine differences in TE in chronically anticoagulated patients managed with heparin bridging therapy relative to oral AC discontinuation or continuation. Patients taking warfarin should be counseled that bridging therapy is probably associated with increased bleeding risks in procedures in general relative to AC cessation (Level B). Bridging probably does not reduce clinically important bleeding relative to continued AC with warfarin in dentistry, but bleeding RDs between patients managed with continued warfarin versus bridging therapy in other procedures are unknown. Given that the benefits of bridging therapy are not established and that bridging is probably associated with increased bleeding risks, there is insufficient evidence to support or refute bridging therapy use in general (Level U).

RECOMMENDATIONS FOR FUTURE RESEARCH

This review highlights limitations in the data related to TE risks in the context of antithrombotic agent discontinuation, theorized rebound effects of antithrombotic medication discontinuation, bleeding risks in invasive procedures, and bleeding risks of some minimally invasive but common procedures. For example, with millions of colonoscopies performed in the United States each year,^{e81} it is critical to understand TE and bleeding risks with different antithrombotic strategies for this procedure.

- Large-scale prospective observational registries of patients receiving antithrombotic agents (whether used individually or in combination) and undergoing minor and major surgical procedures are needed to better define discontinuation risks. Registries should include patients receiving different strategies to highlight various potential risks.
-
- Studies with long-term disability and quality of life endpoints are needed to help understand the relative impacts of bleeding and TE complications.
-
- In minor procedures lacking sufficient evidence, such as endoscopy with regard to AC use, RCTs of antithrombotic agent continuation vs. cessation are needed to better define bleeding risks.
-
- When medications must be stopped, RCTs identifying specifically defined relative bleeding and TE risks associated with different durations of discontinuation are needed to inform the risk–benefit analysis.
-
- RCTs assessing the need for bridging therapy, associated risks, and the ideal method of heparin administration are needed.
-

- Similar studies involving newer ACs such as oral direct thrombin inhibitors and factor Xa inhibitors should be performed.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology*[®] peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

ACKNOWLEDGMENTS

The authors would like to thank Thomas S. D. Getchius and Erin Hagen for their extensive support during guideline development and Stanley N. Cohen, MD, and Cathy Sila, MD, for assistance with abstract review in early guideline development.

REFERENCES

- e1. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993;329:673–682.
- e2. Oscarsson A, Gupta A, Fredrikson M, et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. *Br J Anaesth* 2010;104:305–312.
- e3. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. *Arch Neurol* 2005;62:1217–1220.
- e4. Garcia Rodriguez LA, Cea Soriano L, Hill C, Johansson S. Increased risk of stroke after discontinuation of acetylsalicylic acid: A UK primary care study. *Neurology* 2011;76:740–746.
- e5. Torn M, Rosendaal FR. Oral anticoagulation in surgical procedures: risks and recommendations. *British journal of haematology* 2003;123:676.
- e6. Wysokinski WE, McBane RD, Daniels PR, et al. Periprocedural anticoagulation management of patients with nonvalvular atrial fibrillation. *Mayo Clinic Proceedings* 2008;83:639–645.
- e7. Jaffer AK, Brotman DJ, Bash LD, Mahmood SK, Lott B, White RH. Variations in perioperative warfarin management: outcomes and practice patterns at nine hospitals. *American Journal of Medicine* 2010;123:141–150.
- e8. Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Archives of Internal Medicine* 2008;168:63–69.
- e9. Grip L. Hypercoagulable state and thromboembolism following warfarin withdrawal in post-myocardial-infarction patients. *Eur Heart J* 1991;12:1225–1233.
- e10. Krishnan B, Shenoy NA, Alexander M. Exodontia and antiplatelet therapy. *J Oral Maxillofac Surg* 2008;66:2063–2066.
- e11. Ardekian L. Does low-dose aspirin therapy complicate oral surgical procedures? *J Am Dent Assoc* 2000;131:331–335.
- e12. Partridge CG, Campbell JH, Alvarado F. The effect of platelet-altering medications on bleeding from minor oral surgery procedures. *J Oral Maxillofac Surg* 2008;66:93–97.
- e13. Napenas JJ, Hong CH, Brennan MT, Furney SL, Fox PC, Lockhart PB. The frequency of bleeding complications after invasive dental treatment in patients receiving single and dual antiplatelet therapy. *J Am Dent Assoc* 2009;140:690–695.
- e14. Assia E. Effect of aspirin intake on bleeding during cataract surgery. *J Cataract Refract Surg* 1998;24.
- e15. Shuler JD. Antiplatelet therapy and cataract surgery. *J Cataract Refract Surg* 1992;18:567–571.
- e16. Benzimra JD, Johnston RL, Jaycock P, et al. The Cataract National Dataset electronic multicentre audit of 55,567 operations: antiplatelet and anticoagulant medications. *Eye (Lond)* 2009;23:10–16.
- e17. Kallio H. Haemorrhage and risk factors associated with retrobulbar/peribulbar block; a prospective study in 1383 patients. *Br J Anaesth* 2000;85:708–711.
- e18. Saumier N, Lorne E, Dermigny F, et al. Safety of "needle" regional anaesthesia for anterior segment surgery under antiplatelet agents and anticoagulants therapies. *Ann Fr Anesth Reanim* 2010;29:878–883.
- e19. Kumar N, Jivan S, Thomas P, McLure H. Sub-Tenon's anesthesia with aspirin, warfarin, and clopidogrel. *J Cataract Refract Surg* 2006;32:1022–1025.

- e20. Law SK, Song BJ, Yu F, Kurbanyan K, Yang TA, Caprioli J. Hemorrhagic complications from glaucoma surgery in patients on anticoagulation therapy or antiplatelet therapy. *Am J Ophthalmol* 2008;145:736–746.
- e21. Cobb CJ, Chakrabarti S, Chadha V, Sanders R. The effect of aspirin and warfarin therapy in trabeculectomy. *Eye (Lond)* 2007;21:598–603.
- e22. Oh J, Smiddy WE, Kim SS. Antiplatelet and anticoagulation therapy in vitreoretinal surgery. *Am J Ophthalmol* 2011;151:934–939.e3.
- e23. Otley CC. Complications of cutaneous surgery in patients who are taking warfarin, aspirin, or nonsteroidal anti-inflammatory drugs. *Arch Derm* 1996;132:161–166.
- e24. Bartlett G. Does aspirin affect the outcome of minor cutaneous surgery? *Br J Plast Surg* 1999;52:214–216.
- e25. Billingsley EM. Intraoperative and postoperative bleeding problems in patients taking warfarin, aspirin, and nonsteroidal anti-inflammatory agents: a prospective study. *Dermatol Surg* 1997;23:381–385.
- e26. Kargi E. Complications of minor cutaneous surgery in patients under anticoagulant treatment. *Aesthetic Plast Surg* 2002;26:483–485.
- e27. Shalom A. Outcome of aspirin use during excision of cutaneous lesions. *Ann Plast Surg* 2003;50:296–298.
- e28. Dixon AJ, Dixon MP, Dixon JB. Bleeding complications in skin cancer surgery are associated with warfarin but not aspirin therapy. *British Journal of Surgery* 2007;94:1356–1360.
- e29. Lynch SL, Boon AJ, Smith J, Harper CM, Tanaka EM. Complications of needle electromyography: hematoma risk and correlation with anticoagulation and antiplatelet therapy. *Muscle Nerve* 2008;38:1225–1230.
- e30. Herth FJF. Aspirin does not increase bleeding complications after transbronchial biopsy. *Chest* 2002;122:1461–1464.
- e31. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJF. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. *Chest* 2006;129:734–737.
- e32. Hui AJ. Risk of colonoscopic polypectomy bleeding with anticoagulants and antiplatelet agents: analysis of 1657 cases. *Gastrointest Endosc* 2004;59:44–48.
- e33. Shiffman ML. Risk of bleeding after endoscopic biopsy or polypectomy in patients taking aspirin or other NSAIDs. *Gastrointest Endosc* 1994;40:458–462.
- e34. Yousfi M. Polypectomy lower GI bleeding; potential role of aspirin. *Am J Gastroenterol* 2004;99:1785–1789.
- e35. Sawhney MS, Salfiti N, Nelson DB, Lederle FA, Bond JH. Risk factors for severe delayed postpolypectomy bleeding. *Endoscopy* 2008;40:115–119.
- e36. Hui CK. Does withholding aspirin for one week reduce the risk of post-sphincterotomy bleeding? *Aliment Pharmacol Ther* 2002;16:929–936.
- e37. Hussain N, Alsulaiman R, Burtin P, et al. The safety of endoscopic sphincterotomy in patients receiving antiplatelet agents: a case-control study. *Aliment Pharmacol Ther* 2007;25:579–584.
- e38. Halliwell OT, Yadegafar G, Lane C, Dewbury KC. Transrectal ultrasound-guided biopsy of the prostate: aspirin increases the incidence of minor bleeding complications. *Clin Radiol* 2008;63:557–561.

- e39. Kariotis I, Philippou P, Volanis D, Serafetinides E, Delakas D. Safety of ultrasound-guided transrectal extended prostate biopsy in patients receiving low-dose aspirin. *Int Braz J Urol* 2010;36:308–316.
- e40. Nielsen JD. The effect of low-dose ASA on bleeding after transurethral prostatectomy. *Scand J Urol Nephrol* 2000;34:194–198.
- e41. Ala-Opas M. Blood loss in long-term aspirin users undergoing thransurethral prostatectomy. *Scand J Urol Nephrol* 1996;30:203–206.
- e42. Horlocker TT. Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. *Anesth Analg* 1995;80:303–309.
- e43. Horlocker TT. Risk assessment of hemorrhagic complications associated with nonsteroidal anti-inflammatory in ambulatory pain clinic patients undergoing epidural steroid injection. *2002* 2002;95:1691–1697.
- e44. Manning BJ. The effect of aspirin on blood loss and transfusion requirements in patients with femoral neck fractures. *Injury* 2004;35:121–124.
- e45. Foss NB, Kehlet H. Hidden blood loss after surgery for hip fracture. *J Bone Joint Surg Br* 2006;88:1053–1059.
- e46. Thaler HW, Frisee F, Korninger C. Platelet aggregation inhibitors, platelet function testing, and blood loss in hip fracture surgery. *J Trauma* 2010;69:1217–1220; discussion 1221.
- e47. Kennedy MT, Roche S, Fleming SM, Lenehan B, Curtin W. The association between aspirin and blood loss in hip fracture patients. *Acta Orthop Belg* 2006;72:29–33.
- e48. Nydick JA, Farrell ED, Marcantonio AJ, Hume EL, Marburger R, Ostrum RF. The use of clopidogrel (Plavix) in patients undergoing nonelective orthopaedic surgery. *J Orthop Trauma* 2010;24:383–386.
- e49. Boogaarts HD, Verbeek AL, Bartels RH. Surgery for carpal tunnel syndrome under antiplatelet therapy. *Clin Neurol Neurosurg* 2010;112:791–793.
- e50. Nandoe Tewarie RD, Bartels RH. The perioperative use of oral anticoagulants during surgical procedures for carpal tunnel syndrome. A preliminary study. *Acta Neurochir (Wien)* 2010;152:1211–1213.
- e51. Ferraris VA. Aspirin usage and preoperative blood loss in patients undergoing unexpected operations. *Surg Gynecol Obstet* 1983;156:439–442.
- e52. Mackinnon B, Fraser E, Simpson K, Fox JG, Geddes C. Is it necessary to stop antiplatelet agents before a native renal biopsy? *Nephrol Dial Transplant* 2008;23:3566–3570.
- e53. Atwell T. Pancreas transplants: experience with 232 percutaneous US-guided biopsy procedures in 88 patients. *Radiology* 2004;231:845–849.
- e54. Atwell TD, Smith RL, Hesley GK, et al. Incidence of bleeding after 15,181 percutaneous biopsies and the role of aspirin. *AJR Am J Roentgenol* 2010;194:784–789.
- e55. Sharma AK, Ajani AE, Hamwi SM, et al. Major noncardiac surgery following coronary stenting: when is it safe to operate? see comment. *Catheterization & Cardiovascular Interventions* 2004;63:141.
- e56. Chu EW, Telem DA, Chernoguz A, Divino CM. Assessing the risk of clopidogrel-related bleeding complications in patients undergoing inguinal herniorrhaphy. *Hernia* 2011;15:31–35.
- e57. Chernoguz A, Telem DA, Chu E, Ozao-Choy J, Tammaro Y, Divino CM. Cessation of clopidogrel before major abdominal procedures. *Arch Surg* 2011;146:334–339.
- e58. Ozao-Choy J, Tammaro Y, Fradis M, Weber K, Divino CM. Clopidogrel and bleeding after general surgery procedures. *Am Surg* 2008;74:721–725.

- e59. Cerfolio RJ, Minnich DJ, Bryant AS. General thoracic surgery is safe in patients taking clopidogrel (Plavix). *J Thorac Cardiovasc Surg* 2010;140:970–976.
- e60. Evans IL. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. *Br J Oral Maxillofac Surg* 2002;40:248–252.
- e61. Devani P. Dental extractions in patients on warfarin: is alteration of anticoagulant regimen necessary? *Br J Oral Maxillofac Surg* 1998;58:131–135.
- e62. Al-Mubarak S, Al-Ali N, Abou-Rass M, et al. Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. *Br Dent J* 2007;203:E15; discussion 410–411.
- e63. Sacco R, Sacco M, Carpenedo M, Mannucci PM. Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different intensity targets. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;104:e18–e21.
- e64. Gainey SP, Robertson DM, Fay W, Ilstrup D. Ocular surgery on patients receiving long-term warfarin therapy. *American Journal of Ophthalmology* 1989;108:142.
- e65. Dayani PN, Grand MG. Maintenance of warfarin anticoagulation for patients undergoing vitreoretinal surgery. *Archives of Ophthalmology* 2006;124:1558–1565.
- e66. Alcalay J. Cutaneous Surgery in patients receiving warfarin therapy. *Dermatol Surg* 2001;27:756–758.
- e67. Ihezue CU. Biopsy of the prostate guided by transrectal ultrasound: relation between warfarin use and incidence of bleeding complications. *Clin Radiol* 2005;60:459–463.
- e68. Ruszat R, Wyler S, Forster T, et al. Safety and effectiveness of photoselective vaporization of the prostate (PVP) in patients on ongoing oral anticoagulation. *Eur Urol* 2007;51:1031–1038; discussion 1038–1041.
- e69. McLemore EC, Harold KL, Cha SS, Johnson DJ, Fowl RJ. The safety of open inguinal herniorrhaphy in patients on chronic warfarin therapy. *American Journal of Surgery* 2006;192:860–864.
- e70. Sharifi M, Mehdipour M, Bay C, Emrani F, Sharifi J. Effect of anticoagulation on endothermal ablation of the great saphenous vein. *J Vasc Surg* 2011;53:147–149.
- e71. Krane LS, Laungani R, Satyanarayana R, et al. Robotic-assisted radical prostatectomy in patients receiving chronic anticoagulation therapy: role of perioperative bridging. *Urology* 2008;72:1351–1355.
- e72. Gerson LB, Michaels L, Ullah N, Gage B, Williams L. Adverse events associated with anticoagulation therapy in the periendoscopic period. *Gastrointestinal Endoscopy* 2010;71:1211–1217. e1212.
- e73. Bajkin BV, Popovic SL, Selakovic SDJ. Randomized, prospective trial comparing bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. *Journal of Oral and Maxillofacial Surgery* 2009;67:990–995.
- e74. Repchinsky C, ed. *Compendium of Pharmaceuticals and Specialties*, 2009 ed. Ottawa, ON: Canadian Pharmacists Association, 2009.
- e75. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:299S–339S.
- e76. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke* 1990;21:848–853.

- e77. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology* 2004;62:569–573.
- e78. Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabin J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. *Stroke* 2007;38:3225–3229.
- e79. Lai SM, Alter M, Friday G, Sobel E. A multifactorial analysis of risk factors for recurrence of ischemic stroke. *Stroke* 1994;25:958–962.
- e80. Devereaux PJ, Anderson DR, Gardner MJ, et al. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 2001;323:1218–1222.
- e81. Vijan S, Inadomi J, Hayward RA, Hofer TP, Fendrick AM. Projections of demand and capacity for colonoscopy related to increasing rates of colorectal cancer screening in the United States. *Aliment Pharmacol Ther* 2004;20:507–515.