The implications of statin, beta blocker and anti-platelet agent use on the clinical course of aging patients undergoing surgery are of great importance given the increasing numbers of such patients and the high prevalence and steadily increasing use of these agents in this important demographic. In chronic users, over the past several decades the pendulum has swung from investigations of the implications of whether it was safe to continue them perioperatively to more recent discussions of the potentially adverse effects of stopping them (discussed below). Of the three classes, considerable controversy regarding the ratio of efficacy to safety for cardiovascular outcomes still exists for the anti-platelet agents (outside of the patient with a recently placed coronary stent as delineated in the AHA Periop Guidelines). In higher risk medication naïve patients, there has been considerable investigation into the prophylactic perioperative use of these agents, primarily to reduce perioperative cardiac complications, although evidence for potential efficacy in other organ system complications including renal or sepsis has been presented for the statins. This issue can be further stratified by the presence of either ischemic heart disease or congestive heart failure, conditions that interact significantly together and may have different recommendations for use of these agents in medical guidelines. Finally, within this strata of previously naïve patients, there is some controversy about just how closely to institute therapy prior to surgery, particularly for the beta blockers and statins. In the former group, the primary issue appears to be safety while for the latter it is likely therapeutic effects. There is also interest in potential therapeutic or adverse effects in cerebrovascular disease states (particularly stroke), which occur with lower frequency than cardiac complications but are nonetheless quite serious, particularly in the elderly patient.

The volume of accumulated literature on each of these 3 drug classes multiplied by the “strata” mentioned above (withdrawal, prophylaxis and timing of institution) is very substantial and thus, impossible to present in a short lecture. However, I will attempt to summarize studies and provide the reader with the key references on. Given that age in general is considered by many to be an important covariate in the risk equation for surgery, with several studies supporting its addition as an independent factor independent of the Revised Cardiac Risk Index, and that most of the high risk patients in these studies are in the 60 – 70 year age range, much of the discussion already deals with the “aging patient”. However, where appropriate I will attempt to emphasize age specific issues. Fortunately for all involved (the lecturer and audience), given that so much remains controversial, the current recommendations of the AHA Perioperative Guidelines for Evaluation of the Patient Undergoing Noncardiac Surgery will be emphasized to “keep it simple”. 
Treatment-risk Paradox issue

The medical/cardiology literature has recently emphasized problems associated with use of potentially efficacious medications in the elderly population. A popular concept is that of the “Treatment-Risk Paradox” based on a well-publicized study of statin use in the elderly for secondary prevention in which the likelihood of receiving therapy decreased 6.4% for each year of age increase. 3 Editorial analysis of a recent RCT of a vasodilating beta blocker (nebivolol) in the treatment of heart failure in the elderly (age > 70 yrs) (SENIORS trial) noted that 40% of patients were either unable to tolerate therapy or received lower dosages than which any treatment effect was noted. 4 As well dealing with medication additions or changes in elderly patients where pre-existing cardiovascular polypharmacy, frailty and other comorbidities are present is very challenging.

Alterations in CV physiology and drug handling

A variety of physiologic changes alter the response of the elderly to drugs in general and in the perioperative period. 5 Deterioration in organ function and or responses to stress occur (with wide variability). In particular alterations in the peripheral circulation (decreased distensibility, increased systolic BP) and myocardium (hypertrophy, decreased compliance) and impaired baroreceptor reflexes are well known to anesthesiologists complicating CV control and fluid management. 6,7 Increases in adipose tissue, decreases in body water, muscle mass, creatinine clearance, and possible alterations in hepatic metabolism will generally reduce clearance of drugs in the elderly and often increase sensitivity.

STATINS

The physiologic effects of statins (HMG-CoA inhibitors) include their lipid dependent effects (lowering of LDL cholesterol) to so called pleiotropic effects (lipid independent) which via complex signaling pathways in the endothelium (primarily endogenous Rho and Ras guanosine triphosphatases) improve endothelial function, attenuate inflammatory responses, stabilize atheromatous plaque and decrease thrombotic potential. 8

The safety and effectiveness of statins for medical cardiovascular indications in elderly patients has most commonly been extrapolated from subgroup analyses of large cohort studies of wide age ranges (primary and secondary prevention studies), many of which excluded patients over 75 yrs, and a few specific trials in the elderly (MRC Heart Protection Study, PROSPER, SAGE). 9 The general consensus is that their use is beneficial and when monitored carefully, safe (although findings of an increase in cancer incidence in the PROSPER study have been the subject of some debate). 10 Despite a 2002 AHA Clinical Advisory on the safety of statins which strongly emphasized increased risk in elderly patients and actually recommended withholding of statins (for all patients) during the perioperative period (due to perceived risks for rhabdomyolysis and liver dysfunction), the former issue was not even mentioned in the 2006 AHA Update on Secondary Prevention. 11,12 Thus, the
AHA now takes an aggressive stance towards widespread use of statins. In the perioperative setting, observational reports from the Poldermans group and others have disputed any significant safety issues in vascular patients taking statins. However, a very recent warning was issued by the FDA regarding safety of high dosing of simvastatin (80 mg) in patients not already on it without problem for over one year. As well, there is now strong suggestion that chronic high dose statin therapy is associated with an increased incidence of diabetes (although in high risk patients this risk is considered inconsequential). 13

There has been steadily increasing interest in the perioperative implications of statin use since shortly after the start of the renewed emphasis on beta blockade in the late 1990’s when publication of efficacy in CABG patients was first reported. A very large scale retrospective cohort study by Lindenauer et. al. published in JAMA in 2004 was the first of two (the other being on beta blocker use in the NEJM the following year) to utilize the Premier Perspective proprietary billing administrative database of 329 U.S. hospitals evaluating 780591 patients (2000 – 2001) of whom 9.9% received “lipid lowering” therapy (91% statin use) in the first 3 days of hospitalization. 14 Using propensity matched groups, an odds ratio of 0.62 for reduction of inpatient mortality was observed and the efficacy increased with an increasing number of RCRI variables.

Specific evaluation of the frequency of use of statins in elderly patients in the perioperative period is limited. Hoeks et. al. from the Poldermans group reported a survey of use with in a cohort of 711 vascular surgery patients in 2004, 42% of whom were older than 70 yrs. 15 Statin use (56% overall) was lower in this group (odds ratio 0.6), particularly in the over 80 yr group. In contrast, beta blocker and antiplatelet use were not different between old and younger patients. Statin use was associated with a significant reduction in 1 yr mortality (hazard ratio 0.3), no specific interaction with age was noted. It should be noted that the use of statins since this time has risen substantially, particularly in PVD patients. The Poldermans group has evaluated the efficacy of statins in both observational and randomized trials in vascular and nonvascular cohorts since 2003. 16-23 Probably, their most significant publication is a placebo controlled RCT of nearly 500 vascular patients reported in the NEJM in 2009 of fluvastatin started approximately 37 days preop, which reported reduction in CV death or MI (hazard ratio 0.47) without an increase in adverse events (no reported myopathy or rhabdomyolysis nor elevation of ALT levels). 23 The average age of this cohort was 66 yrs. However, a factorial (2x2) RCT of bisoprolol or fluvastatin in 1066 nonvascular patients (again with mean ages in the mid-60’s) failed to demonstrate a significant reduction in the primary outcome (in contrast to bisoprolol). 22 An observational analysis of 359 vascular pts reported lower rates of ischemia, troponin release and late cardiac events with higher doses of statins. 20

The implications of statin withdrawal in vascular patients were emphasized by Le Manach et. al. in an observational cohort analysis of 669 patients before and after institution of a protocol to ensure early resumption of therapy. Withdrawal for > 4
days was an independent predictor (odds ratio 2.9) for postop MI. More recently they extended observations in 1,674 aortic reconstruction patients reporting reductions in death, MI, CVA and renal failure. Although no reduction was noted in pneumonia, multiorgan failure, or surgical complications, decreased mortality was noted within these strata.

Evaluation of statin use in vascular patients in the United States has been predominantly reported in retrospective observational analyses by vascular surgeons and cardiologists. The results have indicated consistent favorable effects on a variety of outcomes (mortality, MI, graft patency) although not all are consistent across publications. In the new Risk Index proposed by the Vascular Study Group of New England, statin use was not found to be an independent predictor (in contrast to increased risk associated with chronic beta blocker use).

A very recent retrospective observational cohort analysis from Ontario, Canada evaluated older statin users (age > 66 yrs) (prescription data, 90 days of surgery) undergoing major elective surgery (including vascular, thoracic and cardiac), of 213,347 pts. Statin use was associated with lower incidence of acute kidney injury, dialysis (with 14 days of surgery) and mortality (within 30 days).

Most recently, a small prospective clinical study (n = 70 pts) at the Cleveland Clinic evaluated the safety of succinylcholine for induction (1.5 mg/kg) in patients on statins for at least 3 months relative to non users (no specific prospective matching of covariates was done, although some adjustment for unbalanced covariates was performed). A small significant increase in plasma myoglobin was noted as were more intense fasiculations. However, no differences in potassium or creatine kinase or muscle pain was noted.

One retrospective study has reported an increase in delirium in elderly patients receiving statins preoperatively. Redelmeier et. al. using provincial health databases in Ontario, Canada evaluated 284,158 medicare type patients undergoing elective surgery in that province over a decade (1992 – 2002). Using outpatient prescription data and ICD9 chart abstraction data they report an odds ratio of 1.3 for patient receiving statins for postoperative delirium after multiple risk factor adjustment that was not present with the use of 20 other medications. They postulate that statins may predispose to altered cerebral autoregulation via effects on endothelial nitric oxide synthase. These findings have yet to be replicated and are not widely accepted. In contrast, a single center retrospective analysis in Ontario of 528 vascular surgery (2006 – 7) patients reported an increase in delirium with beta blockade, but a decrease with statins (including in a subsequent publication on cardiac surgery patients).

The AHA Periop Guidelines accord Class I level B to continuation of statins in patients chronically taking them, IIa Level B for institution in all vascular patients and IIb Level C for using patients with one risk factor undergoing intermediate risk surgery. They specifically note uncertainty about type, dose and timing of therapy given a relative lack of available RCT data.
BETA BLOCKERS

The effects of aging on beta adrenergically mediated components of the cardiovascular system particularly heart rate, stroke volume and cardiac output continue to be debated and refined in the literature. Many of the studies involved involve response to graded or maximal exercise while others have used catechol stimulation in the resting state. These studies suggested an age related decline in heart rate response. This earlier literature, including several perioperative studies, relied exclusively on isoproterenol given by bolus injection, an approach which is now thought to have elicited a predominance of a reduction in vagally mediated parasympathetic withdrawal in response to beta2 mediated vasodilation. 36 Newer studies using graded steady state infusions of dobutamine (which minimize beta2 stimulation) fail to show a diminished chronotropic response, although a blunted inotropic response does appear to be present. 37,38 Possible differences in receptor density, affinity, and stereoselectivity may also be present but these are controversial. Minor differences noted in a small study of volunteers given atenolol (exercise response) were attributed primarily to aged related decline in renal clearance (recall that atenolol is exclusively renally excreted). 39

The medical literature strongly supports the efficacy of beta blockade in the elderly population for secondary prevention following myocardial infarction and for primary therapy for chronic congestive heart failure. 12,40-42

A full review of the scope of perioperative beta blockade is beyond the scope of this lecture and many of the details are well known to members of this audience. 43-47 In the limited time available we will focus more on the most recent literature published after the latest AHA update. The controversial POISE study, which did demonstrate substantial efficacy in reducing ischemic cardiovascular outcomes (and notably the mean age of that cohort was approximately 69 yrs!), did identify significant safety issues from “aggressive” beta blockade instituted shortly prior to surgery (done for logistical reasons to ensure adequate enrollment and also this was also done in the oft quoted Mangano Atenolol study), particularly with regards to the incidence of clinically significant hypotension which likely contributed substantially to the observed increase in stroke and total mortality (particularly related to sepsis). 48,49 In doing so, this has spurred new research into interactions of beta blockade with acute anemia and potential adverse effects on beta2 mediated cerebral autoregulatory responses (all from the prolific group at the University of Toronto). Thus, beta blocked anemic patients appear to have impaired compensatory responses leading to ischemia. 50 As well, use of metoprolol (which although beta selective is relatively weakly so especially in relation to bisoprolol which Poldermans has used exclusively in his favorable clinical studies) may cause impaired compensatory increases in cerebral blood flow in hemodiluted rats. 51,52

The AHA Periop Guidelines group released a focused update to the existing 2007 guidelines based on the clinical impact and controversy surrounding the POISE study published in 2008. The group took a decidedly conservative turn (in contrast to the newly formed European Society of Cardiology Task Force under the
leadership of Poldermans). The group “downgraded” 1 of the 2 prior Class I indications (use in vascular surgery patients with evidence of ischemia on preoperative testing) with no explanation and “tightened up” the existing statement about continuation of chronic beta blockade specifically in patients with Class 1 AHA indications (note: this excludes patients being treated for hypertension, an area of intense debate at the present time given evidence that their use of primary treatment of HTN is associated with worse long term outcomes, although it is unclear if the AHA group interpreted this as such) and continued the Level C designation based on very limited perioperative data (although this would likely be upgraded to a B if done now). It added what I call the “POISE clause” as a Class III (harm) statement namely not to institute high dose beta blockade in the absence of titration in naïve patients continued the existing Class III statement about administration in presence of “absolute” contraindications (a poorly defined designation) and the rest of the recommendations are in the IIa or IIb categories. The document emphasizes the safety issues identified in the POISE trial and aptly summarizes the risks benefit ratio of heart rate control and strongly recommends gradual preferably dose titrated institution of therapy at least several days prior to surgery. These findings are in line with the recent changes in clinical guideline of the AHA for treatment of both STEMI and NSTEMI in which early use of beta blockade is discouraged in all but the healthiest patients due to a higher incidence of cardiogenic shock and death. 53,54

The POISE-2 trial (www.clinicaltrials.gov) which is enrolling patients at this time (expected completion July 2013) extends on the findings reported in the initial POISE study of beta blockers by switching gears to an alternate sympatholytic agent, clonidine, that perhaps may be safer than beta blockade (although no design papers have yet been published on this and so this is speculative), adding an additional therapeutic arm of attack on perioperative MI, aspirin. The design is a placebo controlled, factorial design randomizing patients to one of the 4 possible combinations of placebo or active agent. Oral clonidine will be given and a patch will be placed 2 – 4 hrs prior to surgery with the patch removed at 72 hrs postop. Aspirin 200 mg will be administered 2 – 4 hrs preop and continued for 30 days in previously naïve patients. The primary outcome is all cause mortality and non fatal MI within 30 days. The study uses the same enrollment criteria as the original POISE study with an estimated sample size of 10,000 patients.

The DECREASE-XIII study is a single center, placebo controlled study evaluating the efficacy of esmolol as an adjuvant to extended release metoprolol in patients undergoing vascular surgery. 55 Patients will be continued on or started on the oral beta blocker per the DECREASE protocol, fluvastatin, aspirin (80 mg) and if indicated by ESC guidelines for CHF, an ACE-I. Esmolol will be instituted intraoperatively if the HR exceeds 80 bpm and continued for 72 hrs postop as indicated by the protocol for 72 hrs postop (along with holter monitoring for ischemia). The primary outcome of this small study (estimated sample size 260 patients) is the total duration of HR outside the target window (60 – 80 bpm) while the secondary outcomes include the major clinical endpoints of cardiac death along
with other measures of ischemia (and thus, the study will be underpowered for them).

Several other RCT's are listed on clinicaltrials.gov using esmolol for hemodynamic control [all funded by Baxter who market esmolol] as well as an old study (not updated since 2007) evaluating CV morbidity in elderly trauma patients.

ANTIPLATELET AGENTS

These agents are used for treatment, primary or secondary prevention in numerous conditions including all manifestations of CAD, cerebrovascular disease, peripheral vascular disease and for prevention of thrombosis in atrial fibrillation, etc. The agents that anesthesiologists are most familiar with include irreversible cyclooxygenase-1 inhibitors (aspirin), reversible COX-1 inhibitors (NSAIDs), the thienopyridines (P2Y12 receptor blockers) (clopidogrel, ticlopidine, prasugrel) and the phosphodiesterase inhibitors (dipyridamole). 56

Most of the emphasis in the perioperative literature has focused on their use in the prevention of either early or late stent thrombosis in patients undergoing surgery following PCI (bare metal or more commonly drug eluting), particularly the use of "dual" therapy with aspirin and a thienopyridine. 57 As well, management of the patient with atrial fibrillation is a common event often requiring heparin "bridging". Over the past decade much research has been done on the safety of NSAID's that have traditionally been felt to be the safest approach to analgesia in many patients but which have now been linked to increased rates of MI and stroke. 58 Recently "black box" warnings for their use following major procedures such as CABG have been issued. Co-administration of NSAIDs with aspirin as also been shown to interfere with aspirin's antiplatelet effects due to competition between the agents for a common docking site within the COX-1 channel. Given the prevalence of chronic pain in the elderly and the primary diseases that aspirin is used for this is a major issue. Aspirin's efficacy has been well demonstrated and its chronic use strongly endorsed for secondary prevention in postMI patients by the AHA. 12 Discontinuation, usually due to non-adherence in the medical population has been very recently shown in a case control study of UK primary care patients (39,513 pts followed for 3.2 yrs) to result in an increase in non-fatal MI (odds ratio 1.63). 59

Despite this enthusiasm, recent literature published in JAMA have cast some doubt on its efficacy in secondary prevention for cardiovascular events in patients with peripheral vascular disease. Berger et. al. presented a meta-analysis reporting a significant reduction in nonfatal stroke but no decrease in CV events. 60 An RCT of 3350 patients with an abnormal ankle brachial index but otherwise free of CV disease randomized to 100 mg aspirin daily followed for 8.2 yrs reported no reduction in vascular events. 61 Despite these findings, it is commonly accepted to be important for PVD patients.

The role of aspirin as a mediator of perioperative thrombotic events is a major focus of clinical research at the present time. The implications of its temporary
withdrawal in those on it chronically or its institution in those naïve to its use are being investigated as noted above by the POISE-2 study and in the studies below.

The DECREASE VII trial will evaluate the efficacy and safety of clopidogrel added to standard treatment in a randomized double blind fashion in vascular surgery patients who have sustained elevation of troponin T within 7 days after surgery. All patients will have received protocol medical therapy of bisoprolol, fluvastatin, aspirin (100 mg/day) and low molecular weight heparin. Treated patients will receive clopidogrel 75 mg qd and aspirin 100 mg qd x 12 months. The primary outcome is a composite of CV death, MI, CVA or medical/surgical intervention for CAD or PAD. The estimated sample size is 750 patients over a period of 4 years. This trial is not yet registered with clinicaltrials.gov and it is unclear if any patients have been enrolled yet.

The OBTAIN study, sponsored by the European Society of Anaesthesiology, is a prospective observational study that will enroll patients having undergone PCI within 4 years of their noncardiac surgery. It will utilize propensity score matching techniques to evaluate the efficacy of either mono- or dual antiplatelet therapy in reducing major adverse cardiac events (MACE) within 30 days of surgery as well as the evaluate safety (bleeding events). An estimated sample size of 1400 patients is being used. The study has not yet started recruiting patients.

The AHA Periop Guidelines make no specific statements regarding the perioperative use of aspirin (or other antiplatelet agents) outside of the patient with prior PCI. It is likely that the scope of recommendations will increase in the coming years when the aforementioned studies are completed and the risk benefit ratio with regards to perioperative bleeding versus reduction of thrombotic CV events is better delineated.

References


