Bridging the gap between clinical trials of antiplatelet therapies and applications among elderly patients

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Although patients aged ≥75 years represent nearly 40% of all those hospitalized with acute coronary syndromes, their enrollment in trials of therapeutic interventions has been relatively modest. Thus, scarce information exists to guide clinicians in decision-making and assessing projections of safety and efficacy for antiplatelet agents. The pathobiology of aging, including age-related changes in vascular repair and integrity, applies to patient management and offers a platform for investigation. Because older patients receive excess dosing of antithrombotic agents much more often than their younger counterparts do, initial steps toward optimized care include attention to indications, dosing, and duration of treatment. This review, representing a summary of information presented at the Fourth Annual Platelet Colloquium held in Washington, DC, in January 2009 and supplemented with recent clinical trial results, underscores an increasingly narrow safety index for antiplatelet agents in the elderly and the all-important balance of safety and efficacy—a dynamic continuum that remains paramount in quality of care. Considerations for future trial designs, registries, and analyses of existing data are highlighted to better guide clinicians toward the optimal management of this rapidly growing, high-risk group. (Am Heart J 2010;159:508-517.e1.)

The elderly (age ≥75 years) represent about 40% of all inpatients with acute coronary syndromes (ACS).[1] Their representation in randomized trials of ACS pharmacotherapies, however, including platelet-directed medications, has historically been low owing to concerns about comorbid conditions and increased bleeding risk. This review, based on information presented at the industry-funded Fourth Annual Platelet Colloquium (see online Appendix for industry sponsorships) held in Washington, DC, in January 2009, centers on parameters and predictors of safety and efficacy associated with the use of antiplatelet agents among elderly patients. It discusses fundamental concepts of platelet biology and hemostasis, pharmacology, and clinical trials as a platform for understanding and overcoming existing barriers to achieving optimal care. Finally, the recent PLATO and CHAMPION trials are discussed to examine whether the knowledge gap is narrowing with respect to antiplatelet therapies and elderly patients.

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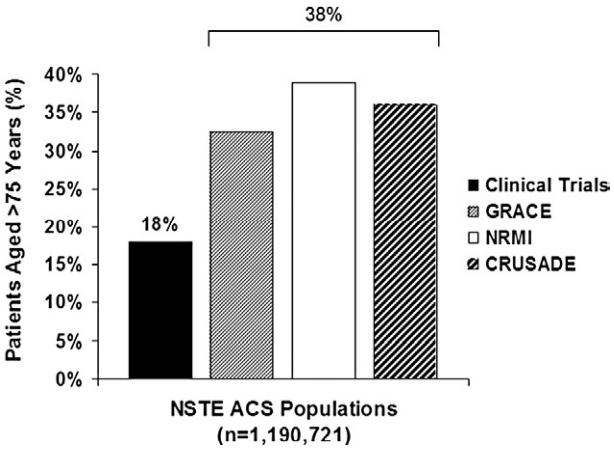
Representation of the elderly in trials of antiplatelet therapy

Heart disease is the leading cause of death among Americans aged ≥75 years,[2] and ~82% of coronary artery disease (CAD)–related deaths in the United States occur in persons aged ≥65 years.[3] In 2 large registries that collectively enrolled 69,000 ACS patients, 32%[4] and 35%[5] of the patients were ≥75 years old. Finally, in a US registry of >1 million patients with ACS, 37% of them were aged ≥75 years.[1]

For this review, we define *elderly* as those aged ≥75 years. Such patients are often systematically excluded from investigations of CAD therapies.[3] In a pooled analysis of large randomized trials of ACS therapies, only 18% of the 34,266 patients enrolled were ≥75 years old (Figure 1).[1] Thus, trial populations underrepresent older patients by about 50% relative to their prevalence in the general ACS population.

Participation of older patients in trials of ACS therapies did not improve over the 1970-2000 period, even as this population segment continued to expand. Between 1996 and 2000, 32% of published randomized ACS trials excluded patients ≥75 years old from enrollment, an identical proportion compared with 1966-1970.[6] Even when elderly patients are included in ACS trials, their enrollment rate is low. As of 2000, >50% of all such trials still failed to enroll a single elderly patient.[6] During the past decade, many ACS trials have continued to lack reports of safety and efficacy outcomes for elderly patients (Table I).[7-22]

Figure 1



Patients aged ≥75 years included in 5 VIGOUR clinical trials versus 3 large community-based registries. Reprinted from Alexander et al[1] with permission.

Excluding the elderly from ACS trials has important clinical implications.[23] Take the case of an 80-year-old man who presents early during acute anterior ST-segment elevation myocardial infarction (STEMI) at a rural hospital without percutaneous coronary intervention (PCI) capabilities. He receives aspirin and a fibrinolytic agent. The CLARITY-TIMI 28 trial showed a 36% reduction in the primary efficacy end point with clopidogrel versus aspirin alone, when given with fibrinolysis as a 300-mg loading dose followed by maintenance dosing of 75 mg daily.[16] Yet this important trial excluded elderly patients, who constitute 30% to 40% of STEMI populations. Although the COMMIT trial examined the daily use of clopidogrel in both young and old STEMI patients, it excluded use of a loading dose.[15] Thus, one cannot infer the safety of loading clopidogrel in elderly patients receiving fibrinolysis.

The TRITON-TIMI 38 trial underscores the clinical significance of including elderly patients in ACS/PCI trials.[13] The overall population derived a significant 19% relative risk reduction for the primary end point (30-day cardiovascular death, nonfatal MI, or nonfatal stroke) with prasugrel versus clopidogrel. Elderly patients (age ≥75 years) constituted only 13% of the overall population.[13] Their 6% relative risk reduction with prasugrel versus clopidogrel was nonsignificant, in contrast to the significant 25% relative risk reduction in younger patients. As discussed below, one might expect platelet-directed therapy to be particularly difficult given the enhanced thrombosis and bleeding risks among elderly patients,[24] reflecting the relationship between aging, the vasculature, and atherothrombosis. The TRILOGY ACS trial of prasugrel versus clopidogrel in ACS patients (NCT00699998) aims to enroll ~25% patients >75 years old, who will receive a reduced dose of prasugrel.

Pharmacodynamic and pharmacokinetic drug responses are altered in elderly versus younger patients, particularly for agents with hypotensive or cerebral effects.[1] Concomitant renal and/or hepatic dysfunction in older persons, with age-related decreases in weight and other comorbidities, can further alter drug responses. Dosing of antiplatelet therapies therefore must be tailored to renal function, weight, and other patient characteristics affecting clearance. In fact, current prasugrel labeling recommends against its general use in patients ≥75 years old,[25,26] although it might be considered at a reduced dose in the elderly and targeted for "high-risk patients (diabetes or prior MI), where its effect appears to be greater."[26] As with many therapies in the elderly, however, the reduced-dose recommendation reflects pharmacokinetic/pharmacodynamic data, not robust clinical trial data.[25]

Aging, hemostasis, and thrombosis

Both thrombotic and hemorrhagic tendencies increase with age.[27] The multifactorial pathobiology of thrombosis and bleeding among the elderly may involve cumulative, chronic vascular injury; defective DNA repair; stem cell exhaustion; and impaired healing capacity as unifying subcellular events. This unique biological paradox reflects the increased levels of procoagulant, anticoagulant, and fibrinolytic factors present in older patients.[27]

Platelet function changes with advancing age. Bleeding times tend to shorten, β-thromboglobulin and platelet factor 4 levels increase, and aggregability in response to adenosine diphosphate and collagen increases.[27] Compensatory responses to oxidative stress become impaired, as do the synthesis of and response to nitric oxide.[28,29] The vascular endothelium also undergoes age-related changes affecting hemostatic integrity (Figure 2).[30] Vessel walls become increasingly rigid; nitric oxide, nitric oxide synthase, prostacyclin, angiotensin II,[30] and the glycosaminoglycan content of vessel walls decrease; and amyloid proteins can deposit in the cerebral circulation (amyloid angiopathy), resulting in both ischemic and hemorrhagic phenotypes.[31]

Classic progeria, a genetic example of accelerated aging, may provide clues to basic mechanisms of vascular metamorphosis. Patients with progeria syndromes have aggressive, disseminated atherothrombosis and progressive degeneration of the skin, muscle, and bone typical of advanced age.[32] Whether the accelerated aging seen with progeria syndromes is similar to normal aging and whether disease models can be used to understand atherothrombosis and hemostasis in older adults require further investigation.

The architecture of the cell nucleus is abnormal in certain premature-aging syndromes (Figure 3).[33] Nuclear

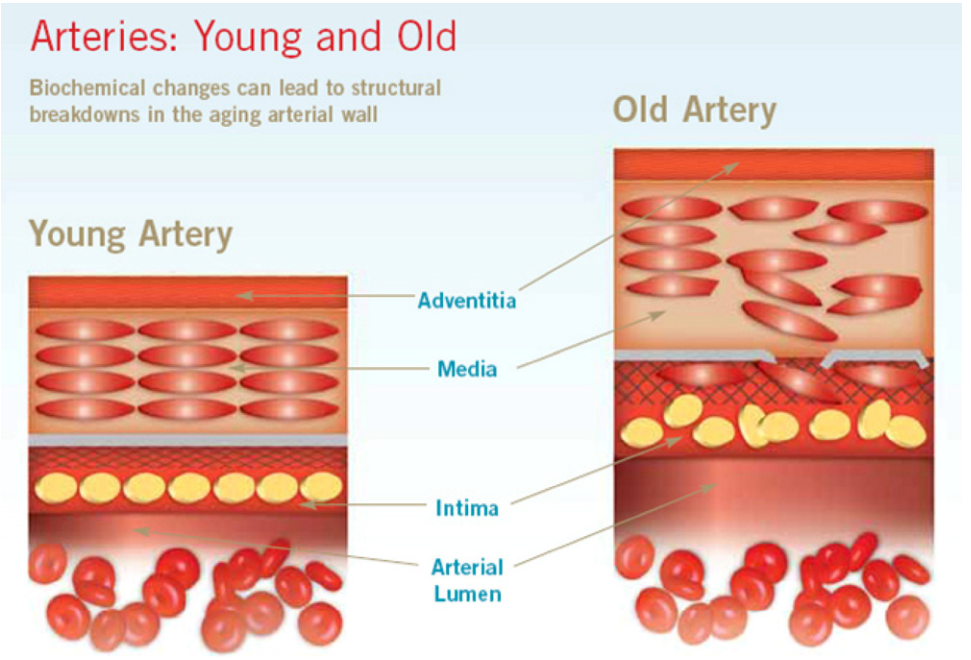
Table I. Safety and efficacy of antithrombotic agents in older patients–selected clinical trials

Drug/study	Population	Age limits	Elderly n (%)	Primary efficacy end point, elderly	Significant bleeding,* overall	Significant bleeding,* elderly
Abciximab						
GUSTO-V[7]	STEMI (fibrinolysis)	Age ≥18 y	Age >75 y 2237 (13%)	Abciximab: 18.3% No abciximab: 17.9% *P* = .83	Abciximab: 4.6% No abciximab: 2.3% *P* < .001	Intracranial bleeding Abciximab: 2.1% No abciximab: 1.1% *P* = .069
ISAR-REACT-2[8,9]	PCI for NSTE ACS	None	Age >70 y 802 (40%)	Abciximab: 10.9% UFH: 9.9% *P* = .65	Abciximab: 1.4% UFH: 1.4% *P* = NS	Abciximab: 2.7% UFH: 1.9% *P* = .46 Transfusions Abciximab: 5.0% UFH: 2.4% *P* = .04
Eptifibatide						
ESPRIT[10]	Stenting for stable angina or NSTE ACS	None	Age ≥65 y nr	Eptifibatide: 6.6% Placebo: 13.7% *P* < .001	Eptifibatide: 1.0% Placebo: 0.4% *P* = .027	Not reported
EARLY-ACS[11]	PCI for NSTE ACS	Age ≥18 y	Age ≥75 y 2377 (25%)	Early eptifibatide: 11.4% Late eptifibatide: 11.4% *P* = NS	Early eptifibatide: 2.6% Late eptifibatide: 1.8% *P* = .015	Not reported
Tirofiban						
PRISM-PLUS[12]	NSTE ACS	None	Age ≥65 y 776 (49%)	Tirofiban + heparin: 17.8% Heparin: 23.5% *P* < .05	Tirofiban + heparin: 3.0% Heparin: 4.0% *P* = .34	Not reported
Prasugrel						
TRITON-TIMI 38[13]	Planned PCI for NSTE ACS	None	Age ≥75 y 1809 (13%)	Prasugrel: 17.2% Clopidogrel: 18.3% *P* = NS	Prasugrel: 2.4% Clopidogrel: 1.8% *P* = .03	Not reported
Clopidogrel						
CURE[14]	NSTE ACS	None	Age >65 y 6208 (49%)	Clopidogrel: 13.3% Placebo: 15.3% *P* < .05	Clopidogrel: 3.7% Placebo: 2.7% *P* = .001	Not reported
COMMIT[15]	Acute MI	None	Age ≥70 y 11934 (26%)	Clopidogrel: 14.9% Placebo: 16.2% *P* = NS	Clopidogrel: 0.58% Placebo: 0.55% *P* = .59	Clopidogrel: 0.84% Placebo: 0.72% *P* = .48
CLARITY[16]	STEMI	Ages 180-75 y	Age ≥65 y 1015 (29%)	Clopidogrel: 19% Placebo: 23.1% *P* = NS†	Clopidogrel: 1.9% Placebo: 1.7% *P* = .80	No increase in bleeding with clopidogrel by age
Bivalirudin						
ACUITY[17,18]	PCI for NSTE ACS	None	Age ≥75 y 2441 (18%)	Bivalirudin: 11.7%‡ Heparin/GPI: 9.6% *P* = NS	Bivalirudin: 3.0% Heparin/GPI: 5.7% *P* < .001	Bivalirudin: 5.8% Heparin/GPI: 10.1% *P* < .05
Cangrelor						
CHAMPION-PCI[19]	Planned PCI	None	Not reported	Not reported	Cangrelor: 0.4% Clopidogrel: 0.3 *P* = .39	Not reported
CHAMPION-PLATFORM[20,21]	NSTE ACS; Planned PCI	Age >18 y	Age ≥75 y 852 (16%)	Not reported	Cangrelor: 0.2% Clopidogrel: 0.3% *P* = .17	Cangrelor: 2.1%§ Clopidogrel: 2.1% *P* = .94
Ticagrelor						
PLATO[22]	STEMI w/planned PCI; NSTE ACS	None	Age ≥75 y 2878 (15%)	Ticagrelor: 16.8% Clopidogrel: 18.3% *P* = NS	Ticagrelor: 11.6% Clopidogrel: 11.2% *P* = .43	Ticagrelor: 14.2% Clopidogrel: 13.3% *P* = NS

NSTE, Non–ST-segment elevation; *NS*, not significant; *UFH*, unfractionated heparin.
* *Nonminor bleeding*, defined as major bleeding by the Thrombolysis In Myocardial Infarction scale, moderate to severe bleeding by the Global Utilization of Streptokinase and TPA for Occluded coronary arteries scale, or other classification system.
† Upper limit of the 95% CI <1.0 for the relative risk of the primary end point with clopidogrel versus placebo.
‡ Composite ischemia end point. Enoxaparin could have been substituted for heparin.
§ Transfusion only, including coronary bypass-related need for transfusion.

malformations observed during normal aging in animal models are similar to those of nuclei from patients with Hutchinson-Gilford progeria syndrome, supporting a hypothesis of altered DNA repair as a mechanism for age-associated vascular change.[34] In progeria syndromes, genetic mutations are responsible for age-

Figure 2



Age-related changes in vascular integrity. Reprinted from the National Institute on Aging.[30]

related vasculopathy; but in "normal" age-associated atherosclerosis and impaired hemostasis, replicative senescence—the so-called Hayflick phenomenon—may be the culprit.[34]

One potential manifestation of genetic instability and resulting vascular changes is abnormal posttranslational processing of lamins, particularly lamins A and C.[35] The lamins, products of the LMNA gene, were originally thought to represent a scaffold for the inner nuclear membrane. LMNA mutations, and resulting disorders in laminar structure and function, have been associated with multiple disorders, including familial partial lipodystrophy and Dunnigan-type dilated cardiomyopathy (Figure 4).[35] The relation between LMNA mutations and clinical manifestations of cardiovascular disorders is being investigated by Duke University Medical Center, using the CATHGEN database.[36]

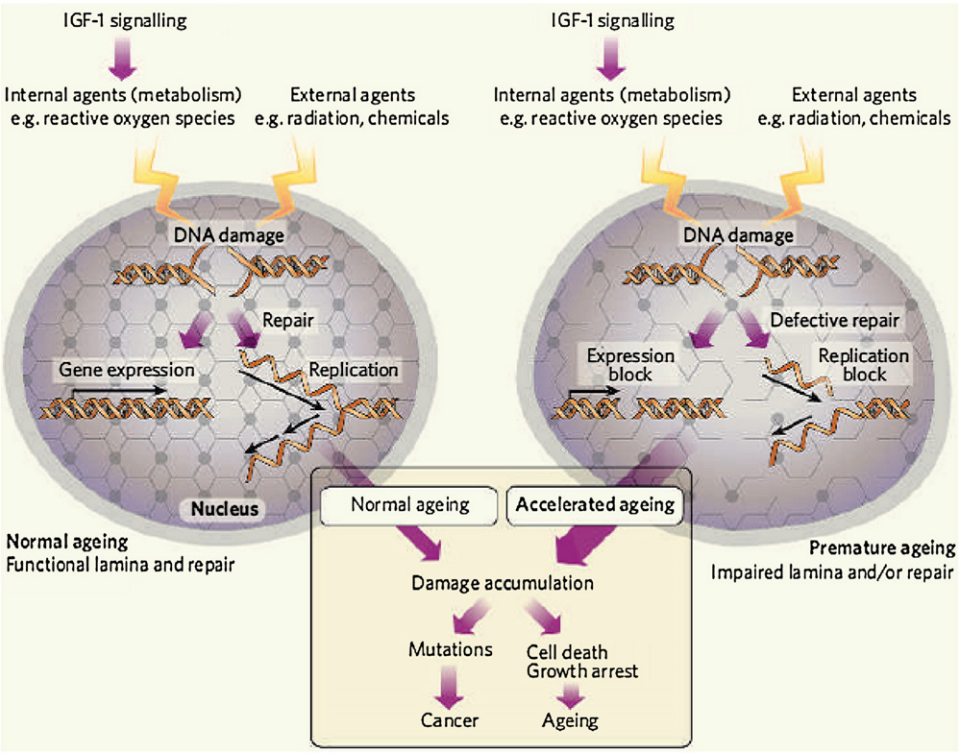
Aging vasculature faces cumulative challenges resulting in impaired hemostatic responses. Whether a response is prothrombotic or prohemorrhagic might partly depend on the affected vascular bed. Impaired regulation of intrinsic thromboresistance in larger vessels could manifest as prothrombotic phenotypes and clinical events. The same operative events in the microvasculature might manifest as integrity loss, vasoreactivity, tissue perfusion, and predisposition to bleeding. These aging-related regulatory impairments provide a framework for concern regarding possibly diminished efficacy and enhanced bleeding risk among elderly patients receiving antiplatelet therapy.

Bleeding risk with antiplatelet therapy in elderly patients

Perhaps because of the age-related vascular changes described above (Table II),[27,33,35,37,38] age has been shown to be an independent predictor of major bleeding in ACS patients.[39-41] Bleeding risk also may be increased in older patients because of comorbidities, such as renal dysfunction and anemia, more prevalent in older patients.[42-45] In analysis of 46,270 patients aged 75 to 89 years and 5,557 patients aged ≥90 years in the CRUSADE registry, major bleeding rates increased significantly as adherence to guideline-recommended therapies (aspirin, heparin, glycoprotein IIb/IIIa inhibitors [GPIs]).[46]

The risk of intracranial hemorrhage (ICH) is particularly high in elderly patients when combining antiplatelet drugs with fibrinolytic agents. In a meta-analysis of 11 randomized trials of fibrinolysis with adjunctive antithrombin treatment, ICH risk was nearly tripled in older patients (defined variously as age >65, ≥70, or ≥75 years) versus younger patients (1.4% vs 0.5%, odds ratio 2.83, 95% CI 2.47-3.24).[47] The GUSTO-V,[7] ASSENT-3,[48] and ASSENT-3 PLUS[49] trials also showed consistently higher ICH risk among elderly patients receiving half-dose fibrinolysis plus intravenous GPI versus fibrinolysis

Figure 3



Age-related alterations in cell nucleus architecture. *IGF*, Insulin-like growth factor. Reprinted from Lans and Hoeijmakers[33] with permission.

alone. Accordingly, the current American College of Cardiology/American Heart Association treatment guidelines recommend against GPI use in elderly patients with STEMI receiving fibrinolysis.[50]

One common but completely preventable cause of bleeding in older patients is excess drug dosing. In a large US registry, ACS patients ≥75 years old were 32% more likely than those <65 years old to receive excess dosing of low–molecular-weight heparin, 34% more likely to receive excess unfractionated heparin, and **6.6 times** more likely to receive excess dosing of GPIs.[51] After adjustment for patient and facility characteristics, the odds ratio for excess dosing of GPIs among the elderly was 14.39,[51] primarily due to lack of adjustment for renal function. Up to 15% of all of major bleedings in the registry (not just among the elderly) might have been attributable to excess antithrombotic dosing.

Table III lists established and potential strategies to reduce bleeding risk in the elderly.[1]

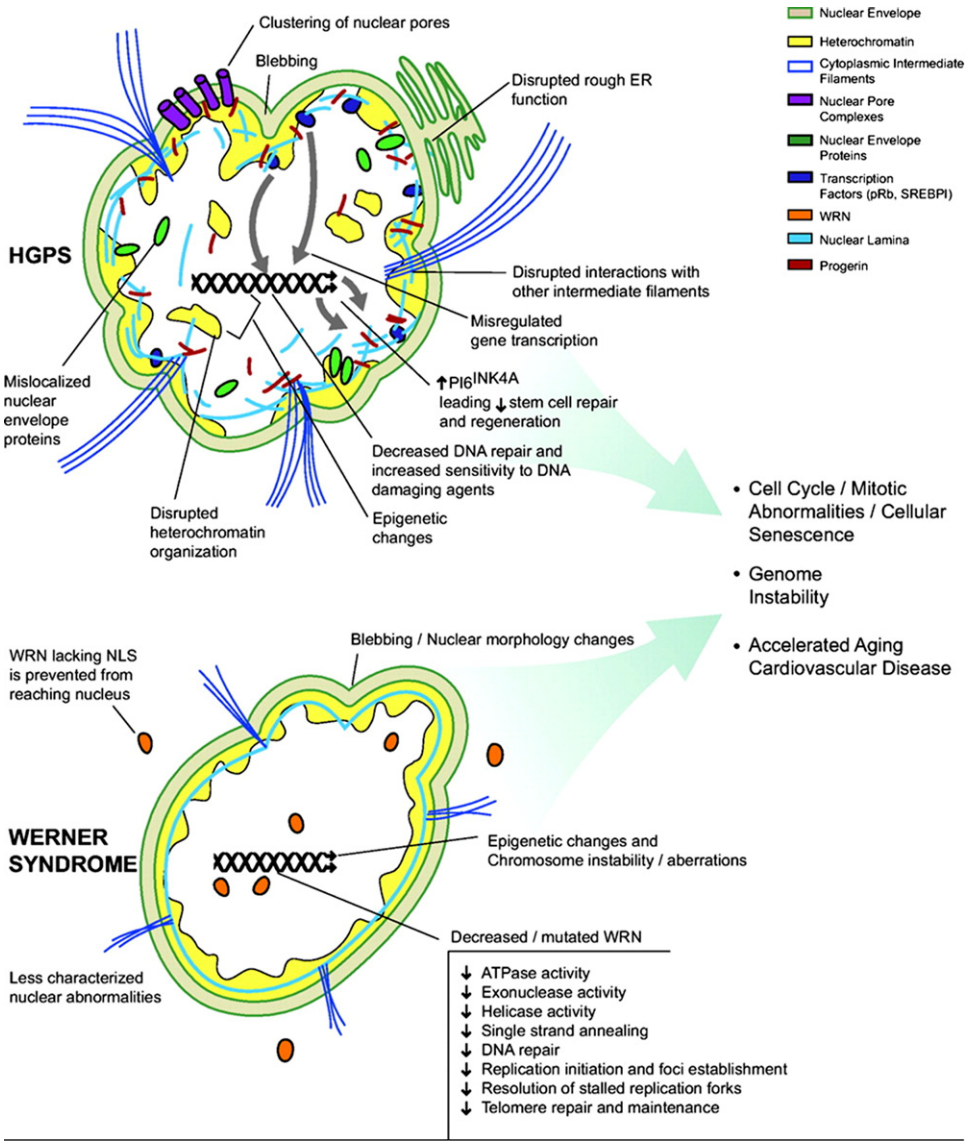
Efficacy of antiplatelet therapy in elderly patients

Table I summarizes the efficacy of antiplatelet agents in patients with various CAD manifestations.[7-22] Only 3 of 13 trials identified significant short-term benefit of antiplatelet therapy among older patients[10,12,14]; 8 noted no significant benefit among the elderly. Given that these trials were underpowered to show efficacy in the elderly, the nonsignificant efficacy results in these patients emphasize the lack of information available to guide decision-making and the necessity to increase their enrollment.

The ISAR-REACT-2 trial compared the safety and efficacy of abciximab and placebo among 2,022 ACS patients undergoing PCI receiving oral antiplatelet therapy.[8,9] In all, 40% of those enrolled were aged ≥70 years. Although younger patients showed a 43% reduction in major adverse cardiovascular events with abciximab, the elderly did not. The interaction between age and efficacy persisted after adjustment for confounding variables.

The ACUITY trial randomized 13,819 ACS patients, not restricted by age, to receive unfractionated heparin or enoxaparin plus GPI, bivalirudin plus GPI, or bivalirudin alone.[17,18] Outcomes were prospectively analyzed among 4 age categories: <55 years (n = 3,655), 56 to 64 years (n = 3,940), 65 to 74 years (n = 3,783), or ≥75 years (n = 2,441, 18% of those enrolled). For all 30-day ischemic outcomes assessed, the interaction between age and treatment was nonsignificant.[17] Bivalirudin use was associated with

Figure 4



Mechanisms for genetic instability in Hutchison-Gilford progeria syndrome and Werner syndrome. *HGPS*, Hutchison-Gilford progeria syndrome; *ER*, endoplasmic reticulum. Reprinted from Capell et al[35] with permission.

significantly less minor and major bleeding compared with heparin plus GPI across all age categories. In fact, the number needed to treat to avoid 1 major bleeding event with bivalirudin alone was lowest in the oldest patients, particularly among those undergoing PCI.[17] The similar efficacy across all ages combined with the increased bleeding rates in the elderly might portend particular significance for bivalirudin use in this population.

Unlike ACUITY and ISAR-REACT 2, many trials cannot assess the efficacy of antiplatelet therapy in older patients because of (*a*) lack of enrollment or (*b*) lack of subgroup analysis by age. Furthermore, the variable definitions of *elderly* have hampered efforts to better establish risk and benefit across trials and registries, with 65,[10,14,16] 70,[8,52] 75,[6,17,53] and 80[54] years representing variable thresholds within the literature. Long-term outcomes data in older patients receiving antithrombotic therapy likewise are sparse. That said, at least 3 trials, GUSTO-V,[55] ESPRIT,[56] and ACUITY,[17] found no significant age-by-treatment interaction for outcomes at 1 year, although ischemic and mortality end point events were increased in all elderly treatment arms.

Finally, because of the lack of elderly-specific trials, physicians must rely on subgroup analyses to assess the

Table II. Factors affecting antiplatelet efficacy and safety in older patients with ACS

Factors that may reduce efficacy	Factors that may increase bleeding risk
• Genetic polymorphisms[37]	• Elevated anticoagulant and fibrinolytic system protein levels[27]
• Elevated clotting factor levels[27]	• Increased sensitivity to effects of anticoagulation, perhaps from increased receptor affinity or lower dietary vitamin K intake[38]
• Elevated β-thromboglobulin and platelet factor 4 levels[27]	• Concurrent use of drugs that increase bleeding risk
• Increased aggregability in response to adenosine diphosphate and collagen[27]	• Associated comorbidity that decreases compliance and/or increases bleeding risk
• Cellular dysfunction from impaired DNA integrity[33]	• Decreased drug clearance (especially renal)
• Abnormal posttranslational processing of lamins[35]	

Table III. Strategies to prevent bleeding complications in elderly patients[1]

Established strategies	Potential strategies
• Adjust dose of GPI, enoxaparin for patients with renal insufficiency	• Reduce dose of chronic prasugrel, or preferential use of clopidogrel
• Consider bivalirudin use for PCI	• Adjust doses of aspirin and clopidogrel based upon point-of-care platelet function assays
• Consider lower-dose aspirin (81 mg) for chronic antiplatelet therapy	• Assess for genetic polymorphisms to characterize potential response to long-term thienopyridine use.
• Avoid triple anticoagulant therapy (aspirin, clopidogrel, warfarin) when possible, including preferential use of bare metal stents to avoid long-term dual therapy during warfarin treatment	• PCI: use radial artery routinely versus femoral artery

clinical efficacy of antiplatelet therapies for the elderly. The dangers of using subgroup analyses to interpret the risk and benefit attributable to patient management are illustrated in the SHOCK trial.[57] Early PCI for cardiogenic shock was associated with significantly reduced 1-year mortality versus intensive medical treatment overall, but this approach was associated with significantly greater mortality among the 56 elderly patients randomized. Subsequent analyses of registry data sets have identified no hazard with aggressive treatment of shock among elderly patients,[53,57-59] suggesting that caution is particularly fitting with small samples and gross underrepresentation of patient subsets.

State of the art and suggestions for future study

Although both the Food and Drug Administration and International Conference on Harmonisation regulations call for analyses of drug safety and efficacy by age to ensure sufficient data for risk assessment, enrollment of older patients in phase 3 trials of ACS therapies remains challenging. These patients are very likely to have real or perceived contraindications to antiplatelet therapy.[23,46,52] Although older patients might derive a proportionally greater overall benefit than younger patients, they also have greater risks of drug-disease and drug-drug interactions—nearly 60% of Americans >65 years old take ≥3 prescription drugs[60]—which can confound analyses of trial data. Dementia and cognitive impairment are more prevalent in older persons, complicating and possibly jeopardizing the ability to obtain informed consent. Finally, practical considerations for older patients on fixed incomes include the extra time, visits, and transportation costs that trial participation may require.

Late in 2009, 3 international phase 3 trials of emerging antiplatelet therapies were published: PLATO, CHAMPION-PCI, and CHAMPION-PLATFORM. Although each sought to include higher-risk ACS patients and did not exclude elderly patients, only 15% of patients enrolled in PLATO and CHAMPION-PLATFORM were elderly. The number of elderly patients in CHAMPION-PCI was not reported, but the median age (~62 years) was similar across all 3 trials, suggesting similar representation of age groups.

The PLATO trial reported both efficacy and safety end points by age subgroup.[22] Patients <75 years old derived a greater relative benefit from ticagrelor treatment (12-month incidence of the primary end point 8.6% with ticagrelor vs 10.4% with clopidogrel, hazard ratio 0.82, 95% CI 0.74-0.91) versus those ≥75 years old (16.8% vs 18.3%, hazard ratio 0.94, 95% CI 0.78-1.12), but the interaction between treatment effect and age category was nonsignificant (P = .22). Similarly, there was no interaction between bleeding and treatment assignment (P = 1.00). There was a 10-fold increase in fatal ICH associated with ticagrelor overall (0.1% vs 0.01%, P = .02), although the drug generally has a favorable safety profile. Analysis of ICH rates among the group at highest risk for such events—elderly patients—would seem to be of especially important concern to clinicians and patients. CHAMPION-PCI did not report safety or efficacy end points for the elderly subgroup. CHAMPION-PLATFORM analyzed safety but not efficacy in the elderly subgroup. The use of transfusions was 3 times more common in elderly versus younger patients, but transfusion use did not differ by treatment (2.1% for both arms).[21]

These 3 trials, representing the state of the art in antiplatelet therapy trials, call investigators to develop strategies to ensure balanced enrollment of older adults, including stratification by age, as trials have done for diabetes status, or prospective requirements for enrollment of a specific proportion of older persons. Medicare began coverage of health care costs for older Americans enrolled in trials in June 2000, partly removing financial barriers to participation. Equally important is a dedicated effort to overcome physician bias against enrollment of elderly patients, as older patients are as likely as younger patients to participate once approached.[61] Finally, exclusion criteria may require modification, given the comorbidities common in the elderly that represent frequent exclusions from ACS and PCI pharmacology trials.[1]

Surveillance of antiplatelet drug safety should not end with regulatory approval. Registries, phase 4 studies, interrogation of large data sets, and systematic adverse-event reporting are critical to detect bleeding, off-target toxicities, and patterns of patient management. Trials should formally analyze age-by-treatment effects to minimize bias introduced by multiple subgroup comparisons. Similarly, meta-analyses are limited by the heterogeneity of trial populations and end point definitions. However, both subgroup and meta-analyses can be used to detect trends in drug safety and efficacy, thereby generating new hypotheses for formal testing. Finally, the altered pathophysiology of aging and its interaction with antiplatelet efficacy must be prospectively determined before committing an ever-growing population of older patients to newer antiplatelet agents.

Conclusions

Elderly patients are underrepresented in clinical research, particularly projects studying ACS and peri-PCI pharmacotherapies. Although selected trials have shown substantial efforts to enroll older patients,[18,9,12,14] the most recent large trials have not maintained this level.[20,21] Even when elderly patients have been enrolled, prespecified subgroup analyses of both efficacy and safety of these agents remain inconsistent. Concerted efforts and strategies for change are needed to achieve the goal of including elderly patients in trial design, enrollment, and follow-up.

The paucity of data challenges even the most skilled clinician when generalizing current trial results to older populations. Several basic questions should be asked of existing guidelines, including the following: (1) Did the cited studies include elderly patients (age $\geq$75 years)? (2) If the elderly were included, did they make up a representative portion of the overall population? (3) If elderly patients were enrolled, were the relevant safety and efficacy findings presented as prospectively identified subgroup analyses?

Although elderly patients are less likely than younger patients to receive guideline-based antiplatelet therapy, clinicians must individualize care given the lack of evidence in common clinical settings.[62] Physicians must pay particular attention to antiplatelet drug choice and dose—being mindful of metabolism, clearance route, and comorbidities that add risk for complications such as bleeding. Translational science, based on models of aging coupled with mechanistic studies running in parallel with clinical trials, represents a strategy with the greatest overall potential for meaningful advances.

References

1. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: non–ST-segment-elevation acute coronary syndromes. Circulation 2007;115:2549-69.
2. Kung HC, Hoyert DL, Xu JQ, et al. Deaths: final data for 2005. Natl Vital Stat Rep 2008;56Hyattsville (MD): National Center for Health Statistics; 2008.
3. American Heart Association. Older Americans and cardiovascular diseases—statistics. Dallas: American Heart Association; 2009.
4. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) project: a multinational registry of patients hospitalized with acute coronary syndromes. Am Heart J 2001;141:190-9.
5. Alexander KP, Roe MT, Chen AY, et al. Evolution in cardiovascular care for elderly patients with non–ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol 2005;46:1479-87.
6. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001;286:708-13.
7. GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition. Lancet 2001; 357:1905-14.
8. Ndrepepa G, Kastrati A, Mehilli J, et al. Age-dependent effect of abciximab in patients with acute coronary syndromes treated with percutaneous coronary interventions. Circulation 2006;114:2040-6.
9. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment. JAMA 2006;295: 1531-8.
10. ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356:2037-44.
11. Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med 2009;360:2176-90.
12. PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non–Q-wave myocardial infarction. N Engl J Med 1998;338:1488-97.
13. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
14. Trial Investigators CURE. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.

15. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-21.
16. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179-83.
17. Lopes RD, Alexander KP, Manoukian SV, et al. Advanced age, antithrombotic strategy, and bleeding in non–ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2009;53:1021-30.
18. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203-16.
19. Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med 2009;361:2318-29.
20. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 2009;361:2330-41.
21. Bhatt DL, Lincoff AM, Gibson CM, et al. Results of the CHAMPION PLATFORM trial. Presented at the American Heart Association 2009 Scientific Sessions, Orlando, Florida, November 14-18; 2009. Abstract 09-LBCT-19955-AHA.
22. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
23. Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non–ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA 2004;292:2096-104.
24. Bhatt DL. Intensifying platelet inhibition—navigating between Scylla and Charybdis. N Engl J Med 2007;357:2078-81.
25. European public assessment report for authorised medicinal products for human use—Efient (prasugrel). Available at http://www.emea.europa.eu/humandocs/Humans/EPAR/efient/efient.htm. Last accessed May 29, 2009.
26. Effient (prasugrel) tablets: highlights of prescribing information. Indianapolis: Daiichi Sankyo Inc. and Eli Lilly and Company; July 2009.
27. Franchini M. Hemostasis and aging. Crit Rev Oncol Hematol 2006;60:144-51.
28. Goswami K, Bhatla BD, Shankar R. Platelet protein damage by free radicals and glycation in vitro: the pathological consequences. Indian J Clin Biochem 2000;15:11-6.
29. Goubareva I, Gkaliagkousi E, Shah A, et al. Age decreases nitric oxide synthesis and responsiveness in human platelets and increases formation of monocyte-platelet aggregates. Cardiovasc Res 2007;75:793-802.
30. Dollemore D. Blood vessels and aging: the rest of the journey. Aging hearts and arteries. Bethesda (MD): National Institute on Aging; 2008.
31. Maia LF, Mackenzie IR, Feldman HH. Clinical phenotypes of cerebral amyloid angiopathy. J Neurol Sci 2007;257:23-30.
32. National Institutes of Health. Fact sheet: progeria. August 2006. Accessed available at www.nih.gov/about/researchresultsforthepublic/Progeria.pdf. Last accessed April 9, 2009.
33. Lans H, Hoeijmakers JH. Cell biology: ageing nucleus gets out of shape. Nature 2006;440:32-44.
34. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res 1961;25:585-621.
35. Capell BC, Collins FS, Nabel EG. Mechanisms of cardiovascular disease in accelerated aging syndromes. Circ Res 2007;101:13-26.
36. Catheterization Genetics (CATHGEN) Web site. About CATHGEN. Available at http://cathgen.duhs.duke.edu/modules/cath_about/index.php?id=1. Last accessed April 9, 2009.
37. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med 2008;360:354-62.
38. Fitzmaurice DA, Blann AD, Lip GYH. Bleeding risks of antithrombotic therapy. BMJ 2002;325:828-31.
39. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-82.
40. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes. J Am Coll Cardiol 2007;49:1362-8.
41. Feit F, Voeltz MD, Attubato MJ, et al. Predictors and impact of major hemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 trial. Am J Cardiol 2007;100:1364-9.
42. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol 2003;92:930-5.
43. Moscucci M, Fox K, Cannon C, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2003;24:1815-23.
44. Voeltz MD, Patel AD, Feit F, et al. Effect of anemia on hemorrhagic complications and mortality following percutaneous coronary intervention. Am J Cardiol 2007;99:1513-7.
45. Dauerman HL, Lessard D, Yarzebski J, et al. Bleeding complications in patients with anemia and acute myocardial infarction. Am J Cardiol 2005;96:1379-83.
46. Skolnick AH, Alexander KP, Chen AY, et al. Characteristics, management, and outcomes of 5,557 patients age ≥90 years with acute coronary syndromes. J Am Coll Cardiol 2007;49:1790-7.
47. Ahmed S, Antman EM, Murphy SA, et al. Poor outcomes after fibrinolytic therapy for ST-segment elevation myocardial infarction: impact of age (a meta-analysis of a decade of trials). J Thromb Thrombolysis 2006;21:119-29.
48. ASSENT-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin. Lancet 2001;358:605-13.
49. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low–molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting. Circulation 2003;108:135-42.
50. Antman EM, Hand M, Armstrong PW, et al. Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. J Am Coll Cardiol 2008;51:210-47.
51. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non–ST-segment elevation acute coronary syndromes. JAMA 2005;294:3108-16.
52. Devlin G, Gore JM, Elliott J, et al. Management and 6-month outcomes in elderly and very elderly patients with high-risk non–ST-elevation acute coronary syndromes: GRACE. Eur Heart J 2008;29:1275-82.
53. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
54. Belkin M, Bhatt DL. Carotid stenting in the elderly: is 80 the new 60? Circulation 2009;119:2302-4.
55. Lincoff AM, Califf RM, Van de Werf F, et al. Mortality at 1 year with combination platelet glycoprotein IIb/IIIa inhibition and reduced-dose fibrinolytic therapy vs conventional fibrinolytic therapy for acute myocardial infarction. JAMA 2002;288:2130-55.
56. O'Shea JC, Buller CE, Cantor WJ, et al. Long-term efficacy of platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention. JAMA 2002;287:618-21.
57. Dauerman HL, Goldberg RJ, Malinski M, et al. Outcomes and early revascularization for patients ≥65 years of age with cardiogenic shock. Am J Cardiol 2001;87:844-8.

58. Dauerman HL, Ryan Jr TJ, Piper WD, et al. Outcomes of percutaneous coronary intervention among elderly patients in cardiogenic shock: a multicenter, decade-long experience. J Invasive Cardiol 2003;15: 380-4.
59. Dzavik V, Sleeper LA, Cocke TP, et al. Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by cardiogenic shock. Eur Heart J 2003;24:828-37.
60. National Center for Health Statistics. Health, United States, 2008. Hyattsville (MD): Centers for Disease Control and Prevention; 2008.
61. Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol 2003; 21:2268-75.
62. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA 2009;301:831-41.

Appendix. Industry sponsorship for and participants in the 2009 Platelet Colloquium

Sponsorship

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