Do Existing Databases Answer Clinical Questions about Geriatric Cardiovascular Disease and Stroke?

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EXECUTIVE SUMMARY

Most randomized, controlled trials evaluating the effectiveness of pharmaceutical, surgical, and device interventions for the prevention and treatment of cardiovascular disease have excluded patients over 75 years of age. Consequently, the use of these therapies in the older population is based on extrapolation of safety and effectiveness data obtained from younger patients. However, there are many registries and observational databases that contain large amounts of data on patients 75 years of age and older, as well as on younger patients. Although conclusions from such data are limited, it is possible to define the characteristics of patients who did well and those who did poorly.

The goal of this conference was to convene the principal investigators of these databases, and others in the field of geriatric cardiology, to address questions relating to the safety and effectiveness of treatment interventions for several cardiovascular conditions in the elderly. Seven committees discussed the following topics:

I. Risk Factor Modification in the Elderly
II. Chronic Heart Failure
III. Chronic Coronary Artery Disease: Role of Revascularization
IV. Acute Myocardial Infarction
V. Valve Surgery in the Elderly
VI. Electrophysiology, Pacemaker, and Automatic Internal Cardioverter Defibrillators Databases
VII. Carotid Endarterectomy in the Elderly

The chairs of these committees were asked to invite principal investigators of key databases in each of these areas to discuss and prepare a written statement concerning the available safety and efficacy data regarding interventions for these conditions and to identify and prioritize areas for future study. The ultimate goal is to stimulate further collaborative outcomes research in the elderly so as to place the treatment of cardiovascular disease on a more scientific basis. (AJGC. 2001;10:207–223) © 2001 CVRR, Inc.
I. RISK FACTOR MODIFICATION IN THE ELDERLY
William R. Hazard, MD; Richard Pasternak, MD; Linda P. Fried, MD, Co-Chairs

Risk factors for cardiovascular disease (CVD) in the elderly, and the evidence that modifying them reduces risk in this age group, were reviewed.

Databases Reviewed
The databases reviewed were drawn from observational studies, randomized clinical trials, and epidemiologic investigations covering a wide range of risk indices, including age, gender, and ethnicity, as well as interventions and approaches to data analysis and interpretation.

Cardiovascular Health Study
This four-community, population-based, 10-year longitudinal observation of over 6000 subjects 65 years of age and older showed the prevalence of both clinical and subclinical CVD to be high (Table I).

Clinical CVD and, with equivalent power, atherosclerotic disease in noncoronary beds, strongly predicted incident events during follow-up, even though the absence of atherosclerosis conferred a low risk of developing CVD. The presence of subclinical coronary heart disease (CHD) portended subsequent CHD with predictive power equal to that of clinical CVD.

While the Cardiovascular Health Study generally confirmed the predictive value of traditional risk factors (with the exception of low-density lipoprotein [LDL] cholesterol, which was predictive only at high levels), CVD, whether clinical or subclinical, was a far more powerful predictor of future events.

Future Priorities
Clinical Assessment. Detection or exclusion of subclinical arterial disease in elderly persons should become a high priority, both in future studies and in clinical practice. The elements of such an assessment are, in sequence of increasing cost:

1 Standardized testing for claudication and angina (Rose questionnaire)
2 Measurement of the ankle-brachial (blood pressure) index (abnormal: ≤0.9)
3 Detection of major resting electrocardiographic abnormalities according to the Minnesota code
4 Echocardiographic evaluation of left ventricular wall motion and aortic patency
5 Ultrasonographic detection of >80% common and internal carotid intimal/medial thickening

The clinical and economic ramifications of accurate assessment of CVD risk in the nearly 50% of older adults with subclinical disease, in whom most of the clinical events will occur, justify the cost of this battery of tests, since preventive interventions can be focused in those at greatest risk.

Clinical Research. No study has yet been designed primarily to accomplish comprehensive risk factor reduction in those over 75. It was the consensus of the participants that such a study would prove risk factor reduction clinically effective, cost-effective, and of acceptable risk.

The risk factors addressed in such a study should be the same as are traditionally highlighted in the nonelderly: hypertension (especially systolic, with elevated pulse pressure), smoking, dyslipoproteinemia, and diabetes.

Apart from studies of new agents, consideration of minor changes in target blood pressure levels or pulse pressure as a more predictive index of risk, and possibly nonpharmacologic modes of blood pressure control, no further major studies of hypertension in the elderly need be initiated.

Risk Factor Reduction. When the knowledge regarding reduction of traditional risk factors was reviewed, the Systolic Hypertension in the Elderly Program (SHEP) was highlighted for its focus on the elderly and its demonstration of the effectiveness of low-cost systolic blood pressure control in preventing stroke as well as other CVD events. The hierarchy of evidence placed cigarette smoking cessation and management of hypertension in the forefront of risk factor reduction.

Dyslipoproteinemia. No consensus was reached regarding treatment of dyslipoproteinemia in the elderly. A minority opinion was that, given the extraordinary prevalence and incidence of CVD in the elderly, the demonstrated safety of LDL-lowering drugs (notably statins) in studies that have included significant numbers of elderly subjects, the weak predictive power of lipid levels in the elderly,
and the potential benefits of statins beyond lipid-lowering per se (e.g., direct effects on the arterial wall), it would be reasonable to treat all elderly individuals with statins, regardless of risk factor status (and cost notwithstanding). The majority favored focusing hypolipidemic treatment on the elderly at highest risk according to the National Cholesterol Education Program (NCEP) guidelines, soon to be updated in ATP-III, and modified as necessary when the current studies of hypolipidemic therapy in elderly patients are reported.

**Diabetes.** Diabetes mellitus represents an even greater challenge. A growing number of studies have underscored the major influence of diabetes in increasing CVD risk, and its synergy with other risk factors, including age. However, the efficacy of available hypoglycemic agents in lowering CVD risk remains to be demonstrated in type II diabetes, and the safety profiles of such agents are of special concern in the elderly. The consensus of the panel was to urge reasonable control of glycemia, with emphasis on aggressive management of other CVD risk factors, to prevent CVD events.

**“New” Risk Factors.** Regarding recently identified risk factors (e.g., high-sensitivity C-reactive protein and homocysteine), the panel recommended ongoing surveillance of findings from basic science, epidemiologic, and clinical studies, but no intervention trials to reduce such risk indices in the elderly at this time.

**Physical Activity.** The role of physical activity and fitness in determining CVD risk, risk factor levels, functional status, rehabilitative/tertiary prevention, and longevity in the elderly received major attention, and the potential for an active exercise program to enhance both quality and quantity of life was highlighted.

**Recommendations**

1. A symposium/task force should be convened, under American Heart Association auspices, to consider in depth the topics discussed briefly by this committee. Also, a conference should be sponsored, supported, and attended by both governmental and nongovernmental representatives.

2. Clinical assessment of elderly patients (especially those over 75) should include evaluation for subclinical CVD as well as for traditional risk factor indices; for this to become widely incorporated into clinical practice, the cost of the evaluation must be reimbursed by third-party payers.

3. Primary attention should be given to cigarette smoking cessation in elderly patients, who, though likely to be addicted to nicotine, have a favorable prognosis for quitting.

4. Hypertension should be managed in the elderly, as in the nonelderly, according to contemporary guidelines (currently, the Sixth Report of the Joint National Committee [JNC-VI]).

5. Dyslipoproteinemia should be treated in the elderly according to NCEP-ATP-II/III guidelines.* In this setting, extracoronary clinical CVD, subclinical vascular disease, and possibly diabetes assume special importance in treatment decisions. Reports from ongoing hypolipidemic trials in the elderly should be followed closely.

6. In the interest of reduced risk for CVD, diabetes should be treated according to guidelines for the nonelderly. However, special care should be taken to avoid pharmacologic misadventures—specifically, hypoglycemia and other side effects of antidiabetic agents currently on the market, and also to the polypharmacy to which the elderly are especially predisposed. For now, the primary emphasis in CVD prevention in diabetes should be on improving nonglycemic risk factors.

7. A formal study of physical exercise in the elderly should be designed and executed, with end points to go well beyond CVD risk and risk factors—to function, quality of life, and longevity.

*With due individualized attention to issues of comorbidities and competing risks, patient preferences, social, economic and spiritual issues, and “frailty” (as yet imperfectly defined and understood) that assure ever-increasing relevance to decision-making with advancing age.

**The Risk Factor Modification Working Group**

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II. CHRONIC HEART FAILURE

Michael W. Rich, MD, Chair

The Chronic Heart Failure (CHF) Working Group examined data from eight databases comprising 84,572 subjects. The analyses and discussion addressed specific questions in three domains:

- Epidemiology, risk factors and prognosis
- Diagnostic assessment and therapy
- Quality of life, exercise tolerance, and cost of care

When feasible, an attempt was made to identify differences within each of these domains as a function of age, gender, race, comorbidity, and pathophysiology (systolic vs. diastolic CHF).

Epidemiology, Risk Factors, and Prognosis.

Findings in this domain were remarkably concordant across databases, and included the following key points:

- Both the incidence and prevalence of CHF increase progressively with advancing age, extending into the ninth and tenth decades of life, and these trends are consistent across all racial and gender subgroups.
- Although the incidence of CHF is higher in men than in women at all ages, women constitute an increasing proportion of CHF cases in older age groups, and over 50% of CHF patients over age 75 are female.
- Hypertension and coronary artery disease (CAD) are the most common etiologies of CHF in the elderly, accounting for 70%–80% of cases. CAD is the most common etiology in men, and hypertension in women. Valvular heart disease and other forms of cardiomyopathy account for most of the remaining cases.
- The prevalence of heart failure with preserved left ventricular systolic function (“diastolic” heart failure) increases with age, and accounts for over 50% of cases after age 75.
- The prognosis for CHF declines progressively with age; 2-year mortality rates range from 20%–50% (depending on the population studied) in patients over age 80. In addition, fewer than 25% of patients over 80 survive for 5 years after being diagnosed with CHF.
- In general, the prognosis for CHF is better in women than in men, and better for diastolic than for systolic heart failure.
- Additional analyses are required to more fully characterize the interactions among age, gender, race, pathophysiology, and selected comorbid conditions (i.e., diabetes, renal dysfunction, atrial fibrillation, cerebrovascular disease, cognitive dysfunction, depression, and frailty) with respect to the epidemiology and prognosis of CHF in the elderly.
may be gained from additional analyses of existing databases.

**Quality of Life, Exercise Tolerance, and Cost**

Data on quality of life and exercise tolerance are limited, and no cost data were presented. Although available data are insufficient to permit definitive conclusions, preliminary analyses indicate the following:

- Exercise tolerance declines progressively with age, but the contribution of CHF to this decline requires further study.
- Despite age-related declines in functional capacity and cardiovascular reserve, self-perceived quality of life does not appear to be age-dependent in CHF patients, perhaps reflecting altered expectations and quality of life goals.
- Additional insights into the impact of CHF on quality of life in elderly CHF patients may be gleaned from further analysis of existing databases, particularly the Cardiovascular Health Study and the Digitalis Investigation Group study.
- The effects of specific therapies, both pharmacologic and nonpharmacologic, on quality of life in elderly CHF patients require further study.

**Limitations of Existing Data**

Several important limitations of existing data were identified:

- Diagnostic criteria for CHF and case-finding methodologies were not standardized across databases, and no two databases used precisely the same definition or diagnostic criteria for identifying CHF cases. In part, this limitation reflects the lack of a reliable, objective means for establishing the diagnosis, as well as a lack of consensus on uniform criteria for identifying cases.
- CHF Working Group data derive from diverse sources, including four population-based epidemiologic surveys, three cohort studies, and one randomized clinical trial. Although each database provides a unique perspective on the CHF syndrome, differences in patient populations and data collection methodologies largely preclude systematically combining different datasets.
- In most of the existing databases, the data on left ventricular function and on the presence of important age-related comorbidities (e.g., cognitive dysfunction, depression, cerebrovascular disease, and frailty) are incomplete, which precludes comprehensive analysis of these factors.
- Quality of life assessments are hampered by the lack of a simple, reliable, and clinically useful tool for evaluating quality of life across multiple domains (e.g., physical, mental, and psychosocial functions and global health status), and the development of such an instrument should be given high priority in future research.

**Recommendations**

The following top research priorities were identified (in no specific order):

- Development of standardized operational criteria for diagnosing CHF and defining the syndrome of diastolic heart failure
- Development of a concise instrument for assessing quality of life across multiple domains in elderly persons with or without cardiovascular disease
- Determination of the impact of CHF and its treatment on quality of life, exercise capacity, and cost of care in older patients
- Determination of the effects of specific comorbidities, including diabetes, renal dysfunction, atrial fibrillation, cerebrovascular disease, cognitive dysfunction, depression, and frailty, on the epidemiology, prognosis, response to therapy, and quality of life in elderly CHF patients
- Observational studies and randomized clinical trials designed to evaluate the effects of specific interventions, both pharmacologic and nonpharmacologic, on the clinical course, prognosis, and cost of care in elderly CHF patients. In particular, studies addressing diastolic heart failure and CHF in the very elderly (age 80 and above) are urgently needed

**The CHF Working Group**

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III. CHRONIC CAD: ROLE OF REVASCU-LARIZATION

Eric Peterson, MD; Jerry Reves, MD, Co-Chairs

One of the most common and challenging dilemmas in treating elderly patients with symptomatic CAD is whether or not to perform coronary revascularization. Ideally, this decision should be a collaboration between the patient and the physician, based on the acute risks and long-term benefits of each treatment option. In younger patients, several randomized clinical trials (e.g., the Coronary Artery Surgery Study [CASS] and the Bypass Angioplasty Revascularization Investigation [BARI]) have helped define the appropriateness of revascularization in specific clinical settings. However, the elderly over 75 years of age were generally not represented in these studies. The goal of this working group was to explore existing clinical registries to determine whether data exist regarding the risks and benefits of revascularization in the elderly. Combined, these databases provided the in-hospital outcomes of 161,776 coronary artery bypass surgery and 29,277 percutaneous coronary intervention (angioplasty) procedures performed in patients aged 75 years or older between 1993 and 1998. Unfortunately, considerably fewer data were available for a range of other important outcomes, such as long-term survival, cognitive function, functional status, and quality of life in elderly patients. The findings were as follows.

Use of Coronary Revascularization in the Aged

Clinicians are less willing to refer elderly than younger cardiac patients for revascularization. The use of bypass and angioplasty after myocardial infarction is six-fold lower among patients aged 80 or older than among those aged 65–70 years. Also, regional disparity in angioplasty and bypass use varies by as much as 10-fold across the U.S.

In all databases studied, the use of intervention-al procedures in the elderly has risen over time. In 1990, those aged 75 years or more constituted 14% of all Society of Thoracic Surgery bypass cases; by 1998, this percentage had risen to 21%.

Another trend is an increased willingness to take on higher-risk elderly patients, including those with more severe coronary disease and greater comorbidity. However, it remains the case that the elderly who are referred for revascularization are generally less burdened by comorbidity than those treated medically (making observational treatment comparisons challenging).

Procedural Risks of Bypass and Angioplasty

A curvilinear relationship between advancing age and increasing mortality from bypass and angioplasty procedures was noted consistently in all databases. Comparison of these interventions revealed that bypass carries, on average, a two- to three-fold higher mortality risk than angioplasty across all age groups. For example, the in-hospital mortality risk of angioplasty rose from <1% in 60-year-old patients to 2%–4% in octogenarians. Similarly, the risk with bypass surgery rose from 2%–3% in patients 60 years of age and younger to 5%–8% in octogenarians.

Procedural mortality for bypass surgery and angioplasty in the elderly also declined over time in all of the databases studied. For example, in the Society of Thoracic Surgery database, although the patient population was higher-risk, the mortality rate after bypass in patients 75 years of age or older declined by nearly 20% between 1990 and 1998.

Elderly bypass patients had higher procedural complication rates than those who underwent angioplasty. In particular, bypass patients 75 years of age or older had a 3%–6% risk of a permanently disabling stroke or coma, as compared with a rate of <1% for angioplasty. Importantly, this reported event rate may exclude undetected minor neurologic events. For example, an early clinical study
involving detailed neurocognitive testing disclosed that up to 50% of elderly who underwent bypass had measurable cognitive impairment at hospital discharge. While up to one half of those with initial impairment recovered within 6 months, the cognitive deficits reappeared in many patients during longer-term follow-up and significantly affected their functional status.

Elderly patients' risk of complications and mortality with angioplasty or bypass can be more accurately estimated from their entire risk profile than from their chronologic age alone. Specifically, there was remarkable consistency among the databases regarding the major clinical predictors of procedural complications and mortality; interestingly, the risk factors identified in the elderly were similar to those previously identified in younger patient cohorts. With the use of published risk algorithms, mortality risk for individual patients and procedures can be stratified from event rates of 2%–3% for the "healthy" old to mortality rates exceeding 30% in the aged with multiple risk factors.

Long-Term Benefits of Revascularization in the Aged.

Although the risks of revascularization, particularly of bypass, are higher in the elderly than in younger patients, it is unclear whether the acute risks are counterbalanced by better long-term survival or functional outcomes than are achieved with conservative medical care. As noted previously, there is a paucity of randomized trial data to clarify this issue. One observational study from Duke showed that, among elderly patients with multivessel coronary disease, those who underwent angioplasty or bypass had significantly higher 7-year survival rates than those treated medically. These significant differences persisted even after the treatment comparisons had been adjusted for multiple prognostic factors.

Improvements in quality of life are particularly relevant to elderly patients. However, very limited data are available regarding the effect of revascularization on elderly patients' functional status. Two preliminary single-institution studies have demonstrated that following angioplasty or bypass surgery, the elderly appear to experience equal or greater symptom relief and quality of life improvement than younger patients. While treatment comparisons were tenuous in these observational studies, the data also suggested that in elderly patients, bypass surgery conferred greater improvement in functional outcomes than either angioplasty or medical therapy.

Recommendations

While our review of existing registries provided new insights on the appropriate use of angioplasty and bypass in the elderly, it also highlighted many areas that require further investigation. A full list of these research needs is beyond the scope of this summary, but four priority areas for investigation were proposed:

1  Better measures of “functional health and vitality.”

Throughout our conference, it was repeatedly noted that current severity and comorbidity measures do not adequately characterize "physiologic,” as opposed to "chronologic,” patient age. Simple measures of functional vitality (vs. frailty), such as arm strength tests, 6-minute walk studies, and functional status questionnaires, have high prognostic importance, yet they have not been validated and are underused as prognostic tools, both in research and in clinical practice.

2  Investigation of patient care processes and their influence on revascularization outcomes in the elderly.

Studies of revascularization have lacked adequate elderly representation, resulting in important knowledge gaps. For example, internal mammary artery grafts are used 20% less often in the elderly than in younger patients. Could increased use of these grafts improve elderly bypass outcomes (as they have in younger patients)?

Another question raised during the conference concerns the timing of revascularization. Since the elderly more often have revascularization under urgent or emergent conditions, could earlier, elective use improve outcomes?

The influence of the extent of revascularization on outcomes was also discussed, since some data demonstrate better survival in the elderly after complete than after incomplete revascularization.

Better geriatric care in the postoperative setting might decrease the rates of postoperative delirium and other complications. As newer revascularization technologies enter clinical study (e.g., minimally invasive bypass), we must ensure that sufficient numbers of elderly patients are included.

3  Accumulation of better long-term survival and functional outcome data on the elderly.

Our most glaring deficit regarding revascularization in the elderly centers on whether,
and to what degree, an invasive strategy improves survival and/or functional outcomes. Randomized studies of revascularization vs. conservative medical care should be performed specifically in elderly patients.

Such studies are not only ethically appropriate (given our current lack of knowledge and wide variations in practice), but also of immense public health and economic importance (given the imminent U.S. demographic changes).

In addition to randomized studies, there is a pressing need to expand centers collecting longitudinal survival and functional outcomes for elderly cardiac patients.

4 Better communication with elderly patients concerning treatment risks and benefits. Managing the elderly cardiac patient is rarely a win-win scenario. The elderly patient with multivessel disease faces the lowest short-term risk with conservative care, but may also have the highest long-term symptom frequency and mortality with this option. On the other end of the spectrum, bypass surgery presents the highest acute risk to the patient, but perhaps the most favorable long-term profile. Depending on how patients weigh these potential outcomes, treatment selection may vary considerably. Thus, innovative tools are needed to communicate outcome probabilities to patients and to elicit their preferences.

CONCLUSIONS
Existing clinical data registries contain important information regarding revascularization outcomes in the elderly, and research in this field will be facilitated by cross-collaboration (increasing elderly representation). However, major gaps will remain in our base of knowledge regarding revascularization, particularly in defining which patient subgroups will accrue long-term benefit from intervention. Future research, including randomized trials and expanded long-term observational registries, are strongly encouraged as a means of providing our elderly with a rational, evidence-based approach to revascularization therapy.

The Revascularization Working Group
Gerald O’Connor, PhD; Fred Grover, MD; Edward Hannan, PhD; Ben McCallister, PhD; Mark Newman, MD; William Weintraub, MD; David Malenka, MD; Eric Peterson, MD; and Jerry Reves, MD, were working group members who contributed data to the conference. In addition, John Spertus, MD and Jennie Wei, MD, PhD attended our Washington working group meeting and contributed to the discussion.

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IV. ACUTE MYOCARDIAL INFARCTION
Harlan M. Krumholz, MD; Gary Genstenblith, MD, Co-Chairs

The Acute Myocardial Infarction (AMI) Working Group examined databases comprising more than 600,000 subjects. The group focused on acute presentations and therapies, and did not address issues of secondary prevention. The analyses and discussion addressed the following specific questions:

1 Is AMI a different disease in the elderly, as compared with younger patients? Questions were raised about our basic understanding of the pathophysiology of AMI in the very elderly. The following key points were consistent throughout all databases examined.
   - The incidence of AMI increases progressively with advancing age.
   - The clinical presentation of AMI changes over time, with heart failure a much more common feature with advancing age.
   - The electrocardiographic presentation of AMI changes markedly with increasing age; ST segment depression occurs much more frequently than ST segment elevation.
   - Complications of AMI are much more common in the very elderly.
• The benefit of some therapies seems to diminish with increasing age.
• AMI mortality rates rise dramatically with increasing age.
• Studies of the pathophysiology of AMI (e.g., DeWood’s classic catheterization study) have not included the very elderly.

2 What is the strength of the evidence for “established” therapies for patients over 75 years of age?
• Medications may have different effects in very elderly patients than in younger patients because of differences in cardiac, liver, kidney, gastrointestinal, and cognitive functions, overall frailty, sensitivity to adverse effects, lack of functional reserve, and underlying pathophysiology.
• The evidence for the major therapies was reviewed (Table II).

Only aspirin showed strong evidence for efficacy (what can be achieved under ideal conditions) and effectiveness (what is actually achieved) in the very elderly and earned the highest rating. The other therapies did not show strong evidence of benefit in the very elderly, and the use of these medications can be based only on extrapolation from their effect on younger patients. Evidence from the Cooperative Cardiovascular Project, a large observational study, indicated that thrombolytic therapy is ineffective in the very elderly. General points from this discussion included:
• The evidence for the efficacy and effectiveness of therapies for very elderly patients with AMI is extremely thin.

| Table II. Strength of Evidence for Therapy in Acute Myocardial Infarction in the Elderly |
|---------------------------------------------|-----------------|-----------------|
| RCT | OBSERVATIONAL STRENGTH |
| Aspirin | _ | 4 |
| β Blockers | _ | 2.5 |
| Thrombolysis | +/- | +/- | 1 |
| Primary PTCA | | |
| ACE inhibitors | | N/A | 1 |
| GP IIb-IIIa | N/A | N/A | 0 |
| LMWH | N/A | N/A | 0 |

RCT= randomized controlled trials; strength = ranked from 0 (no evidence)–4 (solid evidence); PTCA= percutaneous transluminal coronary angioplasty; ACE= angiotensin-converting enzyme; GP= glycoprotein; LMWH = low molecular weight heparin

• Randomized trial data for the early use of β blockers in the very elderly do not exist, although some trials suggest that older patients may derive more benefit than younger patients.
• Randomized trial subgroup analyses suggest that early ACE inhibitors are not efficacious in the very elderly.
• Factors influencing the selection of diagnostic and therapeutic strategies in patients over 75 years of age are currently unknown, but insights may be gained from additional analyses of existing databases.

3 In the generation of evidence concerning therapies for the elderly, what is the value of randomized trials vs. observational studies, and of subgroup analysis within the randomized trials?
• The overall results of current randomized trial data may not be relevant to the very elderly.
• Even when age restrictions are not applied to trials, it is likely that the older patients who are enrolled are not broadly representative of older patients seen in practice.
• The environment and protocol of a randomized trial make it more suitable for evaluating efficacy (what can be achieved under ideal conditions) than effectiveness (what is actually achieved).
• Subgroup analyses of older patients within randomized trials are generally part of multiple analyses, and often lack the power to test hypotheses. The trials generally do not enroll enough very elderly patients to test for important age interactions.
• Observational studies are ideal for describing practice patterns, temporal trends, risk factors, and prognosis. For evaluating therapeutic effectiveness, observational studies lack the unique strength of randomization and are more susceptible to bias than are clinical trials. Nevertheless, well conducted observational studies can provide useful evidence about the effectiveness of treatments, and this evidence can inform decisions when trial evidence is not available. Trials cannot be performed for every patient group, and results of observational studies can complement the evidence from randomized trials.

4 For studies of the elderly, what is a clinically meaningful difference in outcome?
The group discussed various cut-points for clinically meaningful differences in outcome
in the elderly. Since event rates for the very elderly are high, small relative reductions in risk can have a substantial benefit. If a meaningful difference is one life saved per 100 patients treated (the standard in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO] trial), that criterion is fulfilled if older patients with a 25% in-hospital mortality rate have only a 4% relative reduction in risk. The challenge of empowering studies to detect such a small relative reduction in risk was discussed, as well as the fact that many studies without a statistically significant benefit are unable to exclude a clinically meaningful difference.

5 In evaluating therapies, what are the best approaches to incorporate patients’ preferences into the care?
Mortality is the central focus of most studies, but many other outcomes deserve attention, particularly in the older age group. Patients do not have a uniform set of preferences about their care and outcomes, but the fundamental importance of health status and satisfaction with care were noted. In addition, end-of-life issues, which few studies have approached, deserve substantial attention for these patients.

Recommendations

The following top research priorities were identified:

1 Why is there excess mortality? There is a need for better understanding of the host, the disease, the response to therapy, and the quality of care for very elderly patients with an AMI.

2 How can we optimize patient outcomes?
   • Better understanding of efficacy and effectiveness of interventions.
   • Incorporation of patient preferences, quality of life, and functional status into outcome assessments for the elderly.
   • Improved prediction models.
   • Insight into issues of resource allocation.
   • Development of better systems of care for older populations.

AMI Working Group
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V. VALVE SURGERY IN THE ELDERLY
Charles McKay, MD, Chair
The Task Force addressed four key questions:
1 What do we need to know regarding valve surgery in the elderly?
What do we know at present?

The Task Force noted that administrative databases have long been used by regulatory agencies and payers to document administrative functions and billing. However, these are not deemed sufficiently accurate or detailed enough to document the decision process for selecting types of care, or the outcomes of these decisions and procedures, in elderly patients with valvular disease.

With respect to processes of care and risks of procedures, documentation of the usefulness of preoperative assessment and the validity of existing guidelines for valve disease in the elderly—especially in the frail elderly—require further evidence, since existing guidelines are based on data taken largely from healthy elderly and middle-aged patients. In particular, the frail elderly have late presentation of symptoms, atypical symptoms, and late referral from primary care practitioners. The referral end points of symptoms vs. abnormalities on noninvasive testing are quite different from those in younger patients.

Most importantly, outcome data with respect to operative processes of care, mortality, the risks of surgery vs. no surgery, and the risk of combined procedures need to be specifically documented in the elderly.

For example, prospective data show that for asymptomatic patients with aortic stenosis and a mean age of 65 years, overall survival without surgery is directly related to the maximum Doppler echocardiographic velocity across the stenotic aortic valve. However, most of these patients were in the middle-aged and young-elderly age range; only about 15% were 75 and older.

The STS database from 1990–1997 shows that the average mortality in over 1 million open-heart procedures varied widely and was related to the complexity of the procedure. The average mortality rates were: with coronary artery bypass surgery (CABG) alone, 2.9%; with CABG plus aortic valve replacement (AVR), 6.8%; and with CABG plus mitral valve replacement (MVR), 13.4%. These databases also showed a distinct age-related increase in mortality for CABG plus AVR; patients between ages 20 and 70 had an average mortality of 3%–4%; those between 71 and 80, 6.7%; those between 81 and 90, 9.4%; and patients over 90, 22.7%.

A survey of the Society for Thoracic Surgery (STS), Veterans Administration (VA) Cooperative Study, and Northern New England databases, clearly shows that existing databases contain records for procedures carried out primarily in patients younger than 75 years of age. For example, in the Northern New England database, of 13,000 patients who underwent AVR, only about 1700 were 75 or older. Thus, any conclusions drawn from this and similar databases, including risk modeling, are limited in terms of managing elderly patients.

The power of age as a predictive factor is compromised by the small number of elderly patients in the database who have undergone AVR. However, we know that age per se has an effect on both operative and late mortality. Data on AVR from STS and the VA Cooperative Study show that both 30-day perioperative mortality and 10-year mortality were related to age and complexity of the procedure. Patients over 65 who underwent AVR with CABG had a 37% 10-year survival, whereas those younger than 65 who had AVR alone had an approximate 70% 10-year survival. To calculate “excess mortality” (observed mortality minus mortality of the general population), survival curves after surgery must be compared to those of a general, age-matched population.

Recommendations

With respect to the need for further data regarding preoperative assessment, it is recommended that:

1. A multicenter, prospective, cohort study be instituted, with a standard preoperative assessment tool and with specific follow-up of the patients’ functional status, quality of life, and limitations by specific comorbidities.

2. A population-based study be undertaken to track, for each patient, the dates of symptom onset, diagnosis, and referral to specialists for further work-up, so that the time before evaluation and decision-making can be analyzed as independent variables. The effects of late referral bias on prognosis, with and without valve replacement, can then be determined.

3. Existing guidelines be modified to address the problem of optimal noninvasive work-up and optimal time to refer elderly and frail elderly patients for subspecialty evaluation and consideration of valve surgery.

4. Clinical databases or registries be implemented that document patients’ decisions to forego or accept surgery, along with their clinical status and comorbidities. The relative risks of delaying or foregoing surgery vs. performing surgery in elderly patients with valvular heart disease will
probably never be studied in a randomized, prospective trial. Such a surgical and nonsurgical database would allow us to capture individual patient decisions and to analyze data from this “experiment of nature.” Patients would be followed prospectively with a specific data instrument after their decisions concerning surgery.

Because valvular heart disease is relatively uncommon, and because the various presenting symptoms and comorbidities further segment the population, randomized, controlled trials are unlikely to answer the questions above. However, well-designed databases and cohort studies are likely to be very useful.

Valve Surgery Working Group
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The survey was faxed and/or e-mailed to individual centers.

Three major U.S. device companies—Guidant, Medtronic and St. Jude—were also contacted to participate in the survey.

Findings

Pacemaker Outcomes. Response to Survey. Of the 25 centers contacted for the survey, nine (36%) responded. Six (67%) provided utilization information for all 5 years surveyed. The other three provided incomplete information for the 5 years. Two provided information on the indications and acute complications related to pacemaker implantation. Only one provided long-term follow-up information with regard to clinical response, complications, and survival. All three device companies had longevity data for all specific leads and generators, but none of the three had clinical information regarding patient outcomes.

Utilization. The number of pacemaker implantations varied significantly among the nine responding institutions. For example, the pacemaker implantation volume for the year 1998 ranged from 41–450. More than 7000 pacemakers were implanted during the 5 years among these nine institutions. Of the total pacemaker population, 20%, 29%, 37%, and 14% were implanted in the <65-year, 65–74-year, 75–84-year, and 85-year age groups, respectively.

Pacing Mode. Among patients who received dual-chamber pacemakers, 45% were age 75 or older, while among those who received single-chamber pacemakers, 58% fell in the “elderly” or “older elderly” age groups. The percentage of dual-chamber pacemakers implanted varied significantly among institutions, from 42%–90% for the year 1998.

Indications. The indications for permanent pacemaker implantation were generally divided into sinus node dysfunction and atrioventricular conduction block. In the group of octogenarians and nonagenarians who underwent permanent pacemaker implantation, the sinus node dysfunction: atrioventricular block ratio was approximately 1:2. The findings generally agree with previously published results, as summarized in the review by Shen and Hayes in 1994.

Acute Complications. Only one institution surveyed provided details of acute complications, defined as complications occurring prior to the hospital discharge during the indexing procedure. Overall complications, including pneumothorax, lead dislodgment, pocket hematoma, and cardiac tamponade, occurred in fewer than 2%–3% of patients over 70 years of age. Procedure-related mortality was estimated at 0.1%. Female gender and the presence of active malignancy were independent predictors of acute complications. Neither age at the time of pacemaker implantation nor the year of implantation was an independent predictor associated with increased risk for acute complications.

Long-Term Outcomes. Long-term survival data were provided by only one institution, for patients who underwent pacemaker implantation from 1980–1992. In this 13-year period, 1661 patients 70 years of age or older received a permanent pacemaker. In the study cohort, the median survival was 6.2 years and the mean follow-up duration, 4.7±3.2 years. The follow-up information was completed between 1997 and 1999. Observed survival at 1, 3, and 5 years was 83%, 67%, and 58%, respectively. Observed survival was significantly less than in the age- and gender-matched Minnesota population.

Dual-chamber pacemaker implantation was an independent predictor for improved long-term survival. Although selection bias was clearly present, patients of advanced age, nursing home residents, and those with paroxysmal atrial fibrillation, angina, cancer, or organic brain syndrome were more likely to receive single-chamber pacemakers, and male patients, in general, to receive dual-chamber pacemakers.

Long-term outcomes with regard to functional and physical performance are not readily available in existing databases. A lack of documentation of long-term pacemaker-related complications was also noted.

ICD Databases. All nine centers that completed the questionnaire had an ICD database. Information uniformly available from all databases comprised patient demographics, indications for implantation, ICD type (with regard to both vendor and to single-vs. dual-chamber status). From 1994–1998, the number of ICD implants increased in each year, both in patients under age 65 and those 65–74. However, this increase was not proportionate in the subpopulation over age 85, in whom the number of implanted ICDs was small. The number of ICDs implanted for ventricular tachycardia increased significantly, while the number implanted after survival of sudden cardiac death remained the same. This proba-
bly reflects a change in management trends due to the results of the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and, more recently, the Multicenter Unsustained Tachycardia Trial (MUSTT). The increase occurred in patients both under and over age 65; thus, if elderly is defined as 65 years of age, there was no difference in management. Use of dual-chamber ICDs has increased since their introduction in 1997.

Acute complications and procedural outcomes especially relevant to the elderly population were, surprisingly, not always reported. Intra- and perioperative complications, which are especially relevant to the elderly population, as well as long-term data regarding symptoms, complications, quality of life, survival, and economic issues, were not well addressed in existing databases.

Summary and Conclusions
The major findings from the survey on existing pacing databases in the elderly are:

1. Utilization information on the number and type of pacemaker are largely available.
2. Indications for pacemaker implantation are often unavailable.
3. The overall complication rate is low, so that an age-dependent difference in acute complications is not apparent. The documented complication rates likely underestimate the actual event rates, due to the lack of a standard recording methodology.
4. Long-term survival data are obtainable. Age at implantation, left ventricular function, New York Heart Association functional class, and number of coexistent illnesses are independent predictors of mortality. Organic brain syndrome, diabetes, age at implantation, year of implantation, and nursing home residency are predictors of VVI pacemaker placement.
5. Outcomes, clinical response, and quality of life data are generally lacking.

Recommendations

1. It is apparent that core data for a standard ICD database have not yet been defined. The definition of the term “elderly” needs revisiting. The aggregate data indicate that 80 years may be more appropriate, since ICD implantation data seem to be similar in all subgroups below this age.
2. A common, standardized database is needed for all pacemaker and ICD implantation centers, incorporating demographics, indications, device types with implantation parameters, complications, and procedural outcomes. Databases with follow-up information should include parameters, complications, device performance, quality of life issues, and survival rates.

BIBLIOGRAPHY


VII. CAROTID ENDARTERECTOMY AMONG THE ELDERLY
Lawrence M. Brass, MD; Jose Biller, MD, Co-Chairs

Carotid endarterectomy (CEA) is a well established strategy for stroke prevention. Clinical trials have proved its effectiveness in patients with both symptomatic and asymptomatic disease. Among appropriately selected patients with high-grade, symptomatic carotid artery stenosis, it is one of the most effective means of stroke prevention.

Low rates of accuracy in diagnostic imaging of carotid stenosis, and high rates of surgical mortality reported in the community, have raised concern about whether the results of CEA trials can be translated into effective therapy in clinical practice. This concern is of particular importance among the elderly, a group commonly undertreated, with a higher rate of surgical morbidity.

Although the risk associated with carotid surgery may increase with age, the risks of carotid atherosclerosis and ischemic stroke are also high in the elderly. The mean age at which stroke occurs in the U.S. is 70 years. Because of the strong association of stroke with age, older patients are commonly considered for endarterectomy. Following publication of the results of the randomized trials, the greatest increase in the use
of endarterectomy occurred in patients aged 70 and older. For those over age 80, the average number of procedures rose by more than 80%.

The goal of this working group was to examine data from the major clinical trials that might provide guidance for the clinical application of CEA among the elderly. The key issues addressed included the risks of the diagnostic evaluation and the procedure in the elderly, the risk of stroke among those who do not have the procedure, the survival rates, and the effectiveness of the procedure.

Extrapolating surgical or stroke risk from clinical trials requires great caution. Trials often exclude patients with comorbid disease, who would be at higher risk for surgical complications, recurrent stroke, and death. Methods of risk or case-mix adjustment have not been established for CEA. Adjustment is needed for symptomatic status, but adjusting for other comorbidities remains problematic.

Extrapolation from clinical trials to older individuals may underestimate the rate of surgical complications. Early studies suggested increased morbidity and mortality for older patients undergoing CEA. During the past decade, reported rates for surgical complications have improved, partly due to direct efforts to improve the outcome of carotid artery surgery. Recent observational reports indicate that older patients are more likely to have comorbidities, such as heart failure or arterial hypertension; however, after adjustment for comorbid diseases, surgical outcomes of CEA appear similar to those in younger patients. At worst, the surgical risk appears only slightly greater among older patients.

When assessing the risk of CEA, it is important to consider more than the surgical risk alone: the total risk to the individual should be considered, including the risk of the diagnostic evaluation (i.e., angiography) and associated surgical risks (i.e., anesthesia). During hospitalization, patients may also experience adverse events not directly related to surgery. The risk of medical complications occurring during hospitalization for carotid endarterectomy are only slightly higher among those age 65 than among younger patients (adjusted hazard ratio, 1.6 in the North American Symptomatic Carotid Endarterectomy Trial [NASCET]).

The risk of CEA must also be weighed against the risk of not having a CEA, which includes suffering a stroke and the likelihood of a stroke being severe, both of which appear to increase with age.

Because of the strong correlation between death and age, the absolute risk of stroke may decrease over time among the very elderly. Death due to causes other than stroke may decrease survival to the point where a high risk of stroke is superceded by an even greater decrease in survival. Although difficult to estimate in individual cases, the 5-year survival for an 80-year-old man is 62%, and for an 80-year-old woman, 72%.

Although analogies are often drawn between coronary artery and carotid artery surgery, we did not consider CABG surgery in our review. Although these vessels may share common pathophysiologic processes, the surgeries and associated morbidities are dramatically different (i.e., major cardiothoracic surgery vs. a procedure that is often done under local or regional anesthesia). In addition, the sensitivities of the end-organs (i.e., brain and heart) to ischemia (and the potential subsequent disabilities) are also dramatically different.

The working group reviewed results, including new analyses, from some of the major CEA trials. These were considered initially in terms of the indication for CEA because of the likely differences in the risk of surgery and the potent differences in the risk of subsequent stroke.

Dr. Virginia Howard presented data from the Asymptomatic Carotid Atherosclerosis Study (ACAS). A subgroup analysis of ACAS (<68 years, n=802 vs. ≥68 years, n=857) suggested that age does not play a major role in outcome. CEA conferred a similar magnitude of risk reduction for those under 68 (60% reduction; 95% CI, 11%–82%) and over 68 (43% reduction; 95% CI, 7% to 70%). Although risk reduction due to CEA appeared to be greater for younger than for older patients, the difference was not statistically significant (p<0.05).

With regard to the perioperative (30-day) event rate by age group in the surgical arm, as seen in Table III, the stroke rate was slightly but not significantly higher in participants over age 75, but overall event rates (stroke, transient ischemic attack, death, and myocardial infarction) were similar across the three age strata. The number of events was very small, so the power of this comparison is relatively low.

Dr. Peter Rothwell presented a combined analysis from the European Carotid Surgery Trialists (ECST), in which the mean age was 62 years (in the NASCET, there was an upper age limit initially, but this was eliminated during the trial and the final mean age was 65). In the Aspirin Carotid Endarterectomy (ACE) trial, the mean age was 69. Among these studies, the rate of stroke following surgery was greater in both symptomatic and asymptomatic (contralateral) carotid arteries older patients. There was no increase in operative risk.

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in the older age groups. The risk in the oldest patients (≥75 years) was nonsignificantly lower than in the younger patients.

Research Priorities
Additional work is needed. Future clinical trials and observational studies of therapy for carotid artery atherosclerotic disease must include more aggressive recruitment of elderly patients. Results must be stratified according to age. Expansion of options for carotid artery imaging raises questions about characterization of carotid pathology (e.g., wall and plaque characteristics), cost-effective application of imaging techniques, and better understanding of their limitations (for example, small fissures seen at surgery are often not seen on images).

In baseline clinical profiles, risk stratification systems are largely lacking, especially for elderly patients. Techniques for risk or case-mix adjustments among surgical institutions also need to be developed and validated. Although the methods of adjustment for risk in endarterectomy are controversial, it is clear that comparison of outcomes must include adjustment for patients' symptom status. In considering outcome, it is important to determine not only the rate, but also the mechanism and severity of subsequent stroke. The appropriateness of CEA has been assessed in several settings, but such evaluation has been relatively neglected in subpopulations who may benefit from surgical therapy but are not evaluated or treated. Data suggest that CEA may be underused, even among ideal candidates.

Finally, new management options for carotid artery disease, such as endovascular techniques, are being introduced and may decrease the need for surgical revascularization or offer less invasive techniques for those who are not surgical candidates.

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<th>Table III. Perioperative Events by Age Group among the 825 Patients Randomized to the Surgical Treatment Arm</th>
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TIA=transient ischemic attack; MI=myocardial infarction

Conclusions
Although surgical risk may be greater among the elderly, age alone does not appear to be a poten risk for surgical morbidity or mortality; much of the risk may be attributable to comorbid conditions. While the risk of stroke and stroke-related disability increases with age, the clinical trials our group reviewed were not designed to provide definitive answers for the elderly and other subgroups. Subgroup analyses should be interpreted with caution; results of even properly conducted subgroup analyses should not be accepted until confirmation is available from other, similar studies. Although additional work is needed, it may be the case that the greatest net benefit of CEA is in appropriately selected older patients. Certainly, on the basis of existing data, age alone should not be considered a contraindication to CEA.

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