News and Views from the Literature

Cholesterol

Children and Cholesterol

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Hyperlipidemia in Children and Adolescents

Valente MV, Newburger JW, Lauer RM.
Am Heart J. 2001;142:433–439.

The National Cholesterol Education Program (NCEP) recommends the selective screening of children and adolescents, targeting those who would be at the highest risk of developing hypercholesterolemia and cardiovascular disease later in life. Screening is recommended for children > 2 years of age and adolescents whose parents or grandparents had angina, myocardial infarction, peripheral or cerebral vascular disease, or sudden cardiac death before the age of 55 years. In addition, testing is also advised for children whose parents have cholesterol levels greater than 240 mg/dL.[1] As cardiologists, we are most directly involved in treating these parents and grandparents and therefore to be in the best position to recommend screening for their progeny. In addition, as "community lipid experts," we are being asked by parents to comment on their children's lipid profiles. This review by Valente and colleagues provides the background to assist the adult cardiologist in assessing the need to direct the child to the appropriate pediatric lipid authority for appropriate treatment.

NCEP classifies a high cholesterol level as being > 95th percentile. This corresponds to a total cholesterol of > 200 mg/dL or low-density lipoprotein cholesterol (LDL-C) > 130 mg/dL.[1]

The initial treatment of high blood cholesterol involves diet with institution of the American Heart Association Step 1 diet, which consists of < 10% of total calories from saturated fat, < 30% of total calories from fat, and < 300 mg of cholesterol per day. If the lipid goals are not achieved, the Step 2 diet is instituted. At this stage, a dietician may be helpful in developing good diet strategies. Regular exercise is also recommended.

If diet is ineffective, pharmacologic treatment is recommended for children older than 10 years of age who have an LDL-C level > 190 mg/dL or an LDL-C level > 160 mg/dL *and* a positive family history of premature heart disease or two risk factors. Because the long-term sequelae of the pharmacologic treatment of hyperlipidemia in children is not clear, the current drugs of choice are the bile acid-binding resins. The known gastrointestinal side effects of these drugs are well known and effect patient compliance. In addition, adverse effects include decreased absorption of vitamins and other medications, and hypertriglyceridemia. Some of these effects may be minimized with the newer generation of bile-acid binding resins (colesevelam). The role of the recently approved selective cholesterol absorption inhibitor, ezetimibe (Zetia®, Merck/Schering-Plough), which avoids the gastrointestinal side effects of the resins, needs to be studied. The use of statins, nicotinic acid, fibric acid derivatives, and probucol is not recommended due to the lack of long-term safety data. Data exists that a variety of pharmacologic approaches have the ability to lower LDL-C; however, there is no data showing that long-term pharmacologic therapy has a positive effect on long-term outcomes. ■

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Angina

Coronary Revascularization for Angina Pectoris in the Elderly

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"The heart that allows life to continue to an advanced age is an organ of rare integrity." [1]

This quotation by two Mayo Clinic physicians made over 60 years ago certainly provides strong testimony to the virtues of a heart that can beat until an old age. Nonetheless, diseases of the heart and vasculature are an all-too-frequent accompaniment of an aging population.[2]

Survival After Coronary Revascularization in the Elderly

Graham MM, Ghali WA, Faris PD, et al.
Circulation. 2002;105:2378–2384.

The Alberta Provincial Project for Outcomes Assessment of Coronary Heart Disease (APPROACH) is a comprehensive database capturing data on all patients undergoing cardiac catheterization in Alberta, Canada since 1995.[2] In this analysis, baseline characteristics and long-term outcomes were obtained from over 6000 patients over 70 years of age and then compared to 15,392 patients under 70 years of age who had undergone cardiac catheterization between January 1995 and 1998.

As expected, the elderly were more likely to have associated comorbidities, to be "sicker," and to have more extensive coronary artery disease and urgent indications for catheterization. Younger patients had a higher frequency of hyperlipidemia. Among patients over 80 years of age, those treated with percutaneous coronary intervention (PCI) and medical therapy had a greater frequency of congestive heart failure and lower ejection fraction; this was not unexpected given that this was a nonrandomized population. Four-year crude survival rates were > 92% for all treatment strategies for patients under 70 years of age. In patients age 70–79 years, 4-year survival was 86.1% for those undergoing coronary bypass surgery (CABG), 87.2% for those treated with PCI, and 81.7% for those undergoing medical therapy. In patients ≥ 80 years of age, survival rates were 83.2%, 77.4%, and 65.7%, respectively. Differences in survival according to treatment strategy were significant ($P \le .0001$) from each group.

Adjusted survival curves using models addressing differences in baseline characteristics demonstrated a significant difference in favor of both forms of revascularization compared to medical therapy. Four-year adjusted actuarial survival rates for CABG, PCI, and medical therapy were 95.0%, 93.8%, and 90.5%, respectively. In 5198 patients age 70–79 years, survival rates were 87.3%, 83.9%, and 79.1%, respectively. In 983 patients age 80 years or older, survival was 77.4% for CABG, 71.6% for PCI, and 60.3% for medical therapy. The greatest relative survival benefit was noted among patients age 80 years or older with the number needed to treat to save one life being 8.9 for PCI and 5.9 for CABG versus 33.1 and 23.4, respectively, in patients under 70 years of age.

One-year mortality rate stratified by treatment, anatomy, and ejection fraction illustrates that the greatest benefit from revascularization on mortality is seen in those patients at higher risk. Using a technique of propensity analysis, which adjusts for the probability of being selected for revascularization and partially adjusts for selection bias, the favorable mortality benefit of revascularization is again evident.

Comment

The management of coronary artery disease in the elderly is complex and challenging. Moreover, the elderly (women in particular) are a subgroup that has been underrepresented in clinical trials. For example, the three early trials of CABG versus medical therapy—namely, the Veterans Administration Cooperative Study, the European Coronary Surgery Study, and the Coronary Artery Surgery Study (CASS)—excluded patients over 65 years of age,[3] yet the median age for CABG in the United States in 1997 was 64.8 years.[4]

Critique

It is important to emphasize that reports from the APPROACH database are subject to all the caveats that apply to nonrandomized trial data. As the authors recognize, statistical adjustment may reduce the impact of selection bias but cannot eliminate it. One has to bear in mind that the poorer results in medically treated patients may reflect, in part, the impact of noncardiac factors on the decision not to perform revascularization. These less-tangible, patient-related factors may be critically important (eg, physiologic vs chronologic age, lifestyle and levels of activity, attitude and expectation, social support, socioeconomic status, and comorbidities). For example, in the Manitoba Longitudinal Study on Aging, self-related health, which reflects the patients' perception of their health status in relationship to others, was a powerful independent predictor of early and late mortality, even after adjustment for objective health status.[5]

Nonetheless, we have learned from the randomized, controlled trials and registry studies that the greatest benefit of CABG over medical therapy on survival is in patients at greatest risk based upon the severity of symptoms and ischemia, the extent and location of coronary artery disease, and the presence of left ventricular dysfunction.[3,6,7]

A similar treatment effect, according to the "gradient of risk" is noted in this study.[2] Nonetheless, the impact of selection bias on outcomes and the choice of therapies has not been eliminated, despite the size of this study and the quality of data, and this applies particularly to octogenarians. On the other hand, it is somewhat reassuring to see the excellent results obtained with PCI and CABG in this large cohort of selected elderly patients.

Demographics

The demographic projections of the elderly in the United States are compelling, and the burgeoning numbers of the elderly are a worldwide phenomenon (Figure 1).[8,9] In 1980, 11% of the U.S. population was age 65 years or older, and this accounted for approximately one third of all health care costs. The U.S. population over age 65 was 16% in 2000 and is estimated to be 30% by the year 2050. Octogenarians are the fastest growing segment of our society and are estimated to number 7 million people in the United States by 2010. It is estimated that in 2040 13 million people will be age 80 years or older, versus 2 million in 1980.[8]

Recent reports are encouraging because it appears that the proportion of elderly who are active and not disabled is increasing.[10] Nonetheless, it must be appreciated that although longevity (as defined by the proportion of the population reaching "old age") is increasing, the maximum age to which humans live has basically been unchanged for centuries. After all, it is said that Ramses II of ancient Egypt was 91 years old when he died, and Michaelangelo was 89 years old. In 1997, the Society of Thoracic Surgeons database documented that 34% of all isolated coronary bypass procedures were in patients age 71 years and older, and 5% were in patients age 81 years and older[4] (Figure 2). The dilemma is readily apparent: as our technical expertise continues to improve, and the utilization of coronary revascularization in patients in their 80s and 90s increases, the emphasis must be on quality of life, and not just survival.

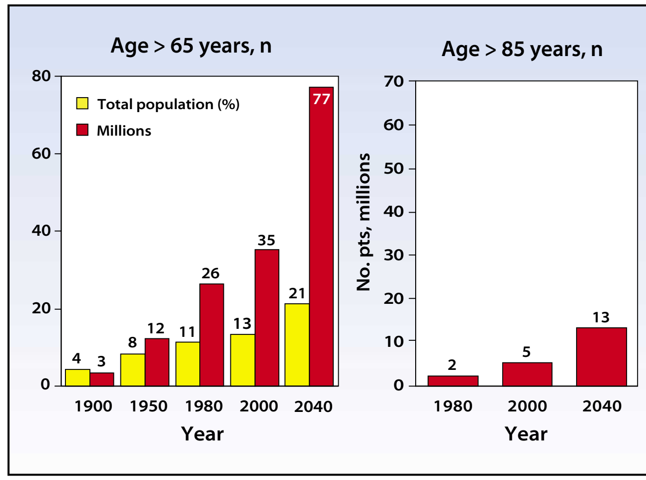


Figure 1. *Demographics of the United States population based upon population projections made by the United States Bureau of Census in 1993. Data from U.S. Bureau of Census.[8]*

Results of CABG and PCI

Multiple studies have demonstrated that the elderly have more severe coronary artery disease and symptoms than younger patients.[11,12] Not surprisingly, periprocedural morbidity and mortality are increased.[11–23] Although this can be accounted for to some extent by indices of disease severity and comorbidity, advanced stage, per se, is an independent predictor of adverse outcomes, both early and late, although it is not the most powerful predictor.[11,19]

The lack of randomized control trial data was alluded to previously, but a subsequent analysis of the CASS Registry emphasized that the gradient of risk applied to older as well as younger patients, in that the benefits of CABG versus medical therapy on survival were noted among those elderly patients at higher risk.[12] Unfortunately, the higher risk subgroup comprised the substantial majority (84%) of the patients age 65 years and older in the CASS Registry (Figure 3). Other studies have emphasized the marked improvement following cardiovascular surgery on quality of life and levels of activity in the elderly.[22] More recently, the Trial of Invasive versus Medical Therapy in Elderly Patients with Chronic Symptomatic Coronary Artery Disease (TIME) which studied CABG/PCI versus medical therapy in 301 patients age 75 years and older with severe angina, showed a reduction in cardiac events and improved quality of life in patients randomized to revascularization.[24] Perhaps this is not surprising because baseline patients were significantly symptomatic, despite medical therapy. Nonetheless, this trial does provide some objective evidence of the benefits of coronary revascularization over medical therapy in the elderly.

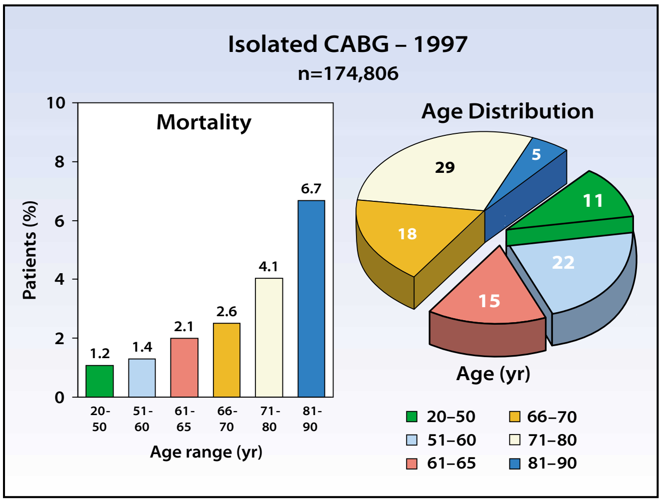


Figure 2. *Perioperative mortality by age group. The mortality of bypass surgery virtually doubles in patients age 71–80 years compared to patients age 61–65 years, and the marked rise in mortality in 81–90-year-olds is noted. Note also that 34% of patients are age 71 years or older and 52% are age 66 years or older. CABG, coronary bypass surgery. Data modified from the Society of Thoracic Surgeons Database.*[4]

Management

Medical therapy for angina pectoris in the elderly is characterized by a substantially higher frequency of drug-induced side effects. The causes are multifactorial and are related, in part, to interactions with other medications that are frequently prescribed in the elderly and the presence of comorbidities, which in turn may complicate the use of cardiac drugs. Other conditions, such as hypertension, diabetes, orthostatic hypotension, postprandial hypotension, underlying conduction disease, and peripheral vascular disease, also create a substrate for adverse drug effects. Moreover, the altered pharmacokinetics of the elderly and the use of polypharmacy mandates careful attention to drug dosing and the timing of administration. Factors such as decreased total body water and lean body mass with increased body fat affect drug distribution, as does the alteration in serum protein levels that may be present due to chronic diseases in the elderly. The latter increases the free-fraction protein-bound drugs, leading to an exaggeration of chemical effects.[25]

In regard to the assessment of the patient for coronary revascularization, the key to a successful early and late outcome is an assessment of the overall patient, and not just the cardiovascular system. For example, comorbidities such as peripheral vascular disease and cardiovascular disease are associated with a substantial increase in the mortality of CABG and PCI, the risk of stroke, and postoperative neurocognitive dysfunction after CABG (Figure 4). Thorough assessment of other organ systems is mandatory, both to identify issues that may complicate the periprocedural period and also to exclude noncardiac factors that may have an adverse impact upon long-term prognosis, such as malignancy.

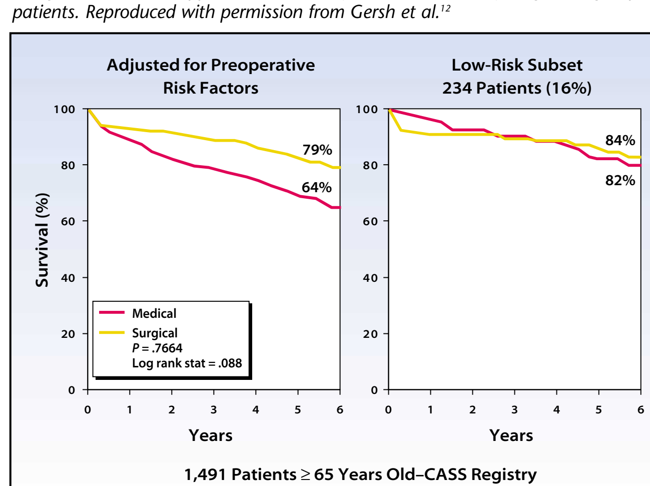
In the elderly, a successful long-term result also depends upon other non-cardiac factors, listed here.

The 5 A's:

- Age (chronologic vs physiologic)
- Activity (level of "normal" activity prior to procedure)
- Attitude (includes an understanding of risks and realistic expectations)
- Associated diseases
- Ability to tolerate medical therapy

The principals of assessing the patient for PCI are basically the same for CABG. The early outcomes of PCI in the elderly are improving even though the patient population is growing older and sicker.[18,23,26] In a recent study based upon the American College of Cardiology's National Cardiovascular Data Registry of 100,243 patients, in-hospital outcomes in 8828 PCI procedures performed on octogenarians were evaluated. Overall, in-hospital mortality was 3.77%, but was only 1.35% in patients who underwent PCI without a recent myocardial infarction. Angiographic success rates were high (93%). In this population, stents were placed in 75% of patients, and the post-PCI length of stay was only 3.3 +/- 5.1 days.[27] Nonetheless, the late results are still characterized by a high rate of recurrent angina, although survival free of subsequent CABG and myocardial infarction is encouraging. A recurrence of angina is likely a reflection of

Figure 3. *Cumulative survival with medical and surgical therapy in nonrandomized patients in the Coronary Artery Surgery Study Registry (CASS). Among the minority of low-risk patients who had mild angina, relatively good ventricular function, and low left main coronary artery disease, there was no survival difference between those treated medically and those treated surgically, whereas surgical survival was significantly improved in the majority of patients who were at high risk. This illustrates that the gradient of risk applies to the elderly as well as to a younger subgroup of patients. Reproduced with permission from Gersh et al.*[12]



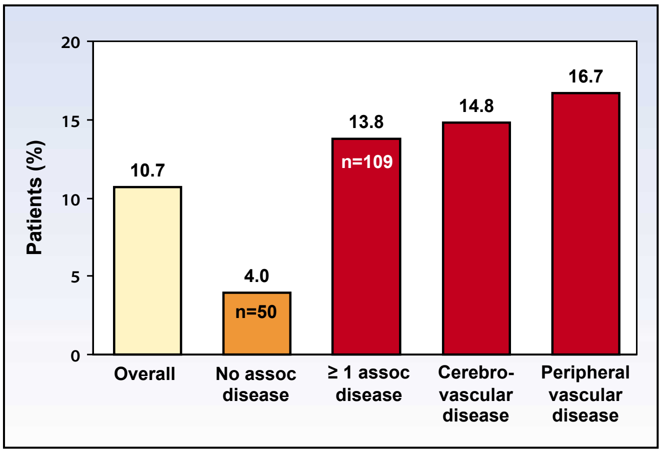


Figure 4. *The overall mortality in 159 patients age 80 years and older at Mayo Clinic undergoing isolated coronary bypass surgery was 10.7%. This was 4% in patients without comorbidities, but the presence of associated disease, and in particular cerebrovascular and peripheral vascular disease, almost quadruple the perioperative mortality. Data modified from Mullany et al.*[19]

diffuse multivessel disease, particularly among patients age 75 years and older.[26]

Summary

In summary, elderly patients comprise a substantial majority of most cardiologists' clinical practice. Future approaches to aging that include genetic breakthroughs are probably many years away, so for the foreseeable future we will be seeing increasing numbers of highly symptomatic patients of advanced age with stable and unstable angina. The judicious use of coronary revascularization that is meticulously evaluated in carefully selected patients certainly enhances the quality of life, and in some subsets, survival is likely improved. Sick, elderly patients offer a window of opportunity for coronary revascularization to have a powerful and satisfying impact upon outcome. Nonetheless, the key to a successful outcome is a strong relationship between the physician, patient, and the patient's circle of support, and to keep in mind the heart is one of many organs afflicted by advancing age. ■

"My diseases are an asthma and a dropsy and what is less curable, age 75." —Samuel Johnson, 1709–1784.[27]

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Stents

Clinical Impact of Stent Design

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Does Stent Design Affect the Probability of Restenosis? A Randomized Trial Comparing Multilink Stents with GFX Stents

Yoshitomi Y, Kojima S, Yano M.
Am Heart J. 2001;142:445–451.

Stent selection is often made using criteria not related to stent design. Stents differ in their metallic composition, strut design (coil, multicellular, slotted tube), length, and presence or absence of coatings, which may alter the performance. Whether the qualities of a particular stent design, including longitudinal flexibility and rigidity, hoop strength, gauge of wire, type of material, and stent surface impact restenosis rates is unclear. An animal model has suggested, for instance, that stent surface material and geometric configuration may be more critical than operator-dependent variables.[1] Do these attributes lead to clinically significant differences in performance, which might cause us to match a specific stent to a particular clinical niche, or are all stents similar enough that non-performance criteria (eg, economic issues, or the presence of a device manufacturing representative in the catheterization lab) play prominent roles?

The study by Yoshitomi and coworkers compares the clinical outcomes of the MULTI-LINK (Advanced Cardiovascular Systems, Guidant, Santa Clara, CA) and GFX (Applied Vascular Engineering, Santa Rosa, CA) stents in a randomized fashion in 100 patients. Quantitative coronary angiography and intravascular ultrasound (IVUS) were performed before, immediately after, and at follow-up (4.2 ± 1.0 months). The MULTI-LINK stent is carved from a stainless steel cylinder and is composed of 12 corrugated rings interconnected by 33 articulations, with a strut thickness of 0.002 inches and a metallic surface area of < 15% after expansion.[2] The GFX stent consists of connected stainless steel segments with a strut thickness of 0.005 inches and a metallic surface area of > 20% after expansion.[2] In the two groups, there were no differences in reference vessel diameter, percent stenosis, lesion length, stent balloon size, and maximal balloon pressure.

This study reinforces the notion that stent design can have an impact on clinically significant events.

Angiographic success and final residual stenosis were the same in both groups. Restenosis occurred in 24% of patients receiving the GFX stent and only 4% receiving the MULTI-LINK stent ($P = .003$). IVUS assessment at follow-up revealed greater maximal in-stent tissue growth and reduced minimal lumen area in the GFX group. There was a trend for reduced 6-month target lesion revascularization rates with the MULTI-LINK versus the GFX stent, but it did not achieve statistical significance (4% vs 13%). In a multiple stepwise logistic regression analysis, the only predictor of restenosis was stent type.

Though neither of these stents are currently commercially available, this study does reinforce the notion that stent design can have an impact on clinically significant events, such as restenosis. Whether the impact of these design differences will no longer be clinically relevant with the advent of drug-eluting stents remains to be seen. In the interim, there does seem to be value in considering issues relating to stent design when matching a particular device to a particular clinical situation. ■

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