SPECIAL ARTICLE

# Cautionary Tales in the Interpretation of Clinical Studies Involving Older Persons

*Ian A. Scott, MBBS, FRACP, MHA, MEd; Gordon H. Guyatt, MD, MSc, FRCPC*

The care of patients 65 years or older presents a challenge for evidence-based medicine. Such patients are underrepresented in clinical trials, are more vulnerable to treatment-induced harm, and often are unable to fully participate in treatment decisions. We outline several cautionary themes in the interpretation of clinical studies of therapeutic interventions involving older persons as they apply to processes of everyday clinical decision making. In particular, we focus on issues of study design and quality of evidence, choice of outcome measures, missing outcome data, assessment of potential harm, quantifying treatment effects in individual patients (and adjusting these for effect modifiers and reduced life expectancy), eliciting patient values and preferences, prioritizing therapeutic goals and selection of treatments, and assisting patients in adhering to agreed therapeutic regimens.

*Arch Intern Med. 2010;170(7):587-595*

Evidence-based medicine (EBM) has been defined as the judicious and systematic application of research evidence to the care of individual patients integrated with clinical judgment, expertise, and patient values and preferences.[1] The care of patients 65 years or older presents a challenge for EBM because these patients are underrepresented in clinical trials.[2] Older patients can exhibit unpredictable treatment responses,[3,4] often experience multiple comorbidities, have restricted life spans, and may be unable to participate in treatment decisions. Only 5% of randomized controlled trials (RCTs) reported in 4 major journals in 2004 were designed specifically for older patients,[5] and 72% of trials reported in 9 major journals between 1994 and 2006 excluded older patients.[6] This exclusion is often poorly justified, especially because most older patients want to participate in clinical trials and because methods for enhancing their recruitment are available.[7]

These limitations have caused some physicians to question the relevance of EBM to the care of older persons.[8-11] If one (inappropriately) regards EBM as synonymous with practice guidelines, one could point to disease-specific guideline recommendations based on evidence that may not apply to older cohorts.[12] Other factors for which it is difficult to blame EBM—pay-for-performance incentives,[13] media influence, pressure from family, and pharmaceutical industry advocacy—may promote potentially inappropriate polypharmacy as physicians are exhorted to deliver care on the basis of "evidence" that may be inapplicable to older patients.[14]

In this article, we discuss several cautionary themes in the interpretation of clinical studies involving older persons, focusing on therapeutic interventions. We relate these themes to everyday clinical decision making[15] and highlight ways in which physicians can more accurately interpret and apply trial results to the care of older persons (**Table 1**).

**Author Affiliations:** Department of Internal Medicine and Clinical Epidemiology, Princess Alexandra Hospital and University of Queensland, Brisbane, Queensland, Australia (Dr Scott); and Departments of Clinical Epidemiology & Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada (Dr Guyatt).

## STEPS IN THERAPEUTIC DECISION MAKING

### Determining the Benefits and Harms of Treatments as Assessed in Clinical Studies

Interpreting evidence from the published literature that addresses the ben-

**Table 1. Decision Steps, Barriers, and Potential Solutions in the Application of Evidence-Based Medicine to Older Populations**

| Decision Steps After Diagnosis | Barriers | Potential Solutions |
|---|---|---|
| What are the relative benefits and harms of potential treatments as assessed in clinical trials? | Underrepresentation of older patients in trials<br>Explanatory study designs limiting generalizability of results<br>Surrogate or invalidated symptom-based outcome measures<br>Loss to follow-up<br>Underreporting of adverse effects | Note trials that exclusively or predominantly enroll older patients.<br>Identify older patient subgroup analyses in trials/reviews.<br>Assume that relative effects are the same and consider older patients' increase in baseline risk.<br>Be aware that characteristics of patients entered into trials may be substantially different from those in clinical practice.<br>Do not trust surrogate outcomes. Be wary of trials in which validity, responsiveness, and interpretability of measures of change in health status have not been established.<br>Consider the vulnerability of trials to show outcomes different from those reported in patients lost to follow-up.<br>Scrutinize trials for their rigor in reporting adverse outcomes. Note population-based, longitudinal studies with adverse event monitoring as the main objective. |
| What are the absolute levels of benefit and harm in my individual patient? | Underreporting of absolute risk (vs relative risk)<br>Unstudied factors that modify treatment effects:<br>-Competing disease risks<br>-Time-dependent changes in risk<br>-Variation in risk-treatment thresholds | Use validated risk prediction rules or scores, and calculate absolute risk reduction.<br>Assess trials for use of expected event-free, quality-adjusted life gain methods in quantifying treatment benefits. |
| What are the values and preferences of my patient? | Limited health literacy and avoidance of decision participation<br>Opinions of surrogate decision makers may not reflect those of patients | Use validated decision aids to aid understanding of risk and benefit.<br>Retrieve population-based studies of elderly health values wherever possible. Critically appraise the validity of surrogate opinions.<br>Adopt consensus approaches that are more likely to give stable, consistent views of patient preferences. |
| What are the treatments that should take priority over others? | Disease-specific clinical practice guidelines may exacerbate the problem of polypharmacy and drug-related adverse events | Retrieve guidelines that focus on older populations and ensure that treatment burden and inconvenience receive adequate consideration in decision making. |
| Will my patient be capable of adhering to treatment? | Uncertainty regarding enablers and barriers to adherence | Use validated adherence-enhancing strategies. |

efits and harms of treatments applied to older patients requires an appreciation of study characteristics that may limit the validity and applicability of their results.

### Study Design and Quality of Evidence

The risk of bias in clinical trials will vary according to study design: randomized trials are much less vulnerable to bias than are observational studies.

### Randomized Controlled Trials

Large pragmatic RCTs[16-20] that have exclusively or predominantly enrolled older patients provide high-quality evidence to inform treatment decisions (**Table 2**). These include drug withdrawal trials that help identify medications that can be safely discontinued in older patients.[21] Because treatment effect may differ across the broad range of ages that fall under the label "elderly," the inclusion in such trials of prespecified age-stratified analyses (eg, 65-74, 75-85, and >85 years) adds further to their information value.

### Meta-analysis of Individual Patient Data From RCTs

Even higher-quality evidence comes from meta-analyses of individual patient data from RCTs with similar study objectives and design wherein results have been stratified according to age. Also of high quality are summary results of aggregated data for age-specific subgroups from systematic reviews or megatrials that involve large numbers of patients. In most cases, such analyses show that treatment effects, usually reported as relative risk (RR) or RR reduction (RRR), do not vary significantly with age. Nevertheless, physicians must be alert to the occasional exceptions where age itself seems to modify treatment effects (**Table 3**).[22-24] It is wisest to assume similar relative treatment effects in older and younger patients unless there is compelling evidence of age-related differences. If differences are seen in subgroup analyses, they are more likely to be real if they meet the following criteria: one of a small number of prespecified analyses, derived from within-trial comparisons, clinically and statistically significant, consistent across studies, and supported by other evidence relating to mechanism of action and physiologic effects.[25]

### Observational Studies

If data from RCTs involving older patients are lacking, physicians must turn to much lower-quality evidence from large observational studies. Here, clinical registries are used to assess treatment effects using multivariate regression models. For example, Setoguchi et al[26] examined 21 484 patients (mean age, 80 years) with myocardial infarction recruited during a 10-year period and found that risk-adjusted mortality declined by 18% in relative terms across 5 years after the index event in response to significantly increasing rates of use of antiplatelet agents (from 3% to 51%), statins (from 8% to 51%), β-blockers (from 42% to

**Table 2. Selected Trials Specific to Older Populations**

| Source | Aims | Study Population | Intervention and Comparator | Outcomes |
|---|---|---|---|---|
| Beckett et al,[16] 2008 | To determine the efficacy of hypertension treatment | 3845 patients aged >80 y with systolic blood pressure of 160-199 mm Hg. Patients with recent stroke, secondary or accelerated hypertension, heart failure, or renal impairment were excluded. | Sustained-release indapamide, 1.5 mg/d vs placebo. If the target blood pressure of 150/80 mm Hg was not achieved, perindopril (2 or 4 mg) or matching placebo could be added. | During mean follow-up of 2.1 y, intervention group vs placebo group had lower rates of fatal stroke (6.5% vs 10.7%), all-cause mortality (47.2% vs 59.6%), heart failure (5.3% vs 14.8%), and any cardiovascular event (33.7% vs 50.6%) ($P<.05$ for all). |
| Shepherd et al,[17] 2002 | To determine the efficacy of statin treatment in patients with, or at high risk for, cardiovascular disease | 5804 patients aged 70-82 y with a history of, or risk factors for, vascular disease. Patients with cognitive dysfunction (Mini-Mental State Examination score <24) were excluded. | Pravastatin, 40 mg/d vs placebo. | During mean follow-up of 3.2 y, intervention group vs placebo group had a 15% lower rate of primary end point (composite of coronary death, nonfatal MI, and fatal and nonfatal stroke), a 19% lower rate of coronary death and nonfatal MI, and a 24% lower rate of coronary death ($P<.05$ for all). Stroke risk was unaffected. |
| Keime-Guibert et al,[18] 2007 | To determine the efficacy of radiotherapy for glioblastoma | 85 patients aged ≥70 y with newly diagnosed anaplastic astrocytoma or glioblastoma. Patients with Karnofsky performance score <70 were excluded. | Supportive care plus radiotherapy (focal radiation in daily fractions of 1.8 Gy given 5 d/wk for a total dose of 50 Gy) vs supportive care alone. | At median follow-up of 21 wk, intervention group vs control group had a 53% decrease in mortality ($P=.002$), with no severe adverse events related to radiotherapy. Results of quality-of-life and cognitive evaluations across time did not differ significantly between treatment groups. |
| Strandberg et al,[19] 2006 | To determine whether better use of preventive methods and treatments of cardiovascular disease reduces cardiovascular events and total mortality | 400 patients aged ≥75 y (mean age, 80 y) with existing cardiovascular disease (previous MI, coronary artery disease, or previous stroke, transient ischemic attack, or peripheral artery disease). | Optimization of pharmacologic and nonpharmacologic cardiovascular treatments by a geriatrician in accordance with current guidelines vs usual care. | At mean follow-up of 3.4 y, there were no significant differences between groups in cardiovascular events or mortality, although serum lipid levels and blood pressure were better controlled in the intervention group. |
| Fletcher et al,[20] 2004 | To determine whether universal multidimensional screening and geriatric team-led management reduces mortality, admissions to the hospital, or quality of life | 43 219 patients aged ≥75 y attending 106 general practices. | Universal vs targeted assessment and subsequent management by a hospital outpatient geriatric team vs a primary care team. Cluster-randomized factorial design. | At mean follow-up of 3 y, there were no significant differences between groups in mortality or in hospital or institutional admissions. Significant improvements in quality of life resulted from universal vs targeted assessment in terms of home care and from management by geriatric teams vs primary care in terms of mobility, social interaction, and morale. |
| Iyer et al,[21] 2008 | To determine whether drugs such as diuretics and psychotropics can be safely withdrawn in selected patients | 448 patients aged ≥65 y living in the community receiving thiazide diuretics (4 RCTs); 697 patients in residential care facilities receiving benzodiazepines (2 RCTs) or psychotropic medications (9 RCTs). Excluded patients were those with stable disease, receiving study drug for at least 6 mo, and who had no active indications for drug continuation. | Continuation of medications or withdrawal for ≥4 wk. | In the thiazide withdrawal trials, 51%-100% of patients could be withdrawn from the drug for 6-52 wk with no adverse effects or rise in blood pressure. In 2 trials, diuretics had to be recommenced because of heart failure, although no information reported on concomitant use of standard antifailure therapies, such as ACE inhibitors and β-blockers. In the benzodiazepine withdrawal trials, no adverse reactions were seen and, in 1 trial, marked reduction in falls was seen (RR=0.34). In the psychotropic withdrawal trials, there was no significant change in behavior or cognition except for 2 trials that reported increased agitation/aggression and poor sleep. |

Abbreviations: ACE, angiotensin-converting enzyme; MI, myocardial infarction; RCT, randomized controlled trial; RR, relative risk.

72%), and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (from 39% to 50%). These same drugs have been shown to be effective in secondary prevention studies involving younger patients.

In an even older cohort, Skolnick et al[27] used data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) registry to study 2 groups of patients with non–ST elevation acute coronary syndromes: those aged 75 to 89 years (n=46 270) and those 90 years or older (n=5557). They found that administering aspirin, β-blockers, and early coronary angiography was associated with the same RRR in in-hospital mortality in both groups; that administering heparin was associated with no effect in either group; and that administering glycoprotein IIB IIIA inhibitors was as-

**Table 3. Selected Analyses That Indicate Variation in Treatment Effect According to Age**

| Source | Trial Description | Results of Whole-Cohort Analyses | Results of Age-Stratified Analyses | Comments |
|---|---|---|---|---|
| Pignon et al,[23] 2009 | To assess whether CABG vs PCI in 7812 patients with multivessel coronary disease reduced all-cause mortality during 6 y | Compared with PCI, CABG was associated with a nonsignificant decrease in deaths (ARR=1%; RRR=9%; *P*=.12). | Individual patient data from 10 trials were analyzed according to age <55 y (n=2185), 55-64 y (n=2933), and ≥65 y (n=2688). The RRR was modified by age with significant RR increase in death from CABG of 25% in patients <55 y, significant RRR of 10% in patients 55-64 y, and significant RRR of 18% in patients ≥65 y. Test for age-treatment interaction was significant (*P*=.002). Treatment effect was not modified by number of diseased vessels or any other baseline characteristic. | Results suggest that, as age increases, outcomes improve with CABG compared with PCI. Younger patients (<55 y) do worse with CABG, patients 55-64 y do better with CABG, and patients ≥65 y derive the best results from CABG. |
| Yusuf et al,[24] 2001 | To assess whether concomitant LRT + CT vs LRT alone in 9615 patients with head and neck cancer improved overall survival during 5.6 y | Compared with LRT alone, LRT + CT was associated with significantly fewer deaths (RRR=19%; ARR=4%). | Individual patient data from 8 trials were analyzed according to age <50 y (n=2584), 50-60 y (n=3306), 61-70 y (n=2698), and ≥71 y (n=692). The RRR was significant for all patients up to and including 70 y (<50 y: 25%; 50-60 y: 23%; 61-70 y: 11%), but in patients ≥71 y, RRR was attenuated and nonsignificant (3%). Test for age-treatment interaction was significant (*P*=.02) and showed a consistent trend (*P*=.003). Treatment effect was not modified by sex, performance status, tumor stage, or site. | Results show that there was a progressive decrease in mortality benefit with increasing age, from 25% in young patients to 3% in the oldest patients. |
| Guyatt et al,[25] 2008 | To assess whether an early invasive strategy vs a conservative strategy in 2220 patients with non–ST-segment elevation acute coronary syndromes reduced the risk of death, nonfatal MI, or rehospitalization for acute coronary syndrome at 6 mo | Compared with the conservative strategy, the early invasive strategy had fewer events (ARR=3.5%; RRR=22%). | Subgroup analysis of this large trial showed that, compared with younger patients, patients ≥65 y showed greater benefit from an early invasive strategy (ARR=5.0% vs 1.8%; RRR=41% vs 22%). This benefit was even greater among those aged >75 y (ARR=10.1%; RRR=42%), for which the age-treatment interaction was significant (*P*=.01). However, this benefit coexisted with a significant 3-fold higher risk of major bleeding in patients aged >75 y (16.6% vs 6.5%). | Results suggest that the efficacy of an early invasive strategy increases with age, but this is offset by an increased risk of major bleeding. |

Abbreviations: ACE, angiotensin-converting enzyme; ARR, absolute risk reduction; CABG, coronary artery bypass graft; CI, confidence interval; CT, chemotherapy; LRT, locoregional treatment; MI, myocardial infarction; PCI, percutaneous coronary intervention; RRR, relative risk reduction.

sociated with an excess number of deaths in the oldest patients.

### Choice of Outcome Measures

Many trials involving older patients assess treatment effect on quality of life (QOL), that is, alleviation of symptoms, cognitive decline, and functional impairment. Such subjective measures rely on patient self-report or that of proxies such as family members and caregivers. Such measures are potentially imprecise and are often not transparent or easily interpretable. The accuracy and reproducibility of QOL measures may not be explicit or formally evaluated. The definition of what informed patients (or proxies) perceive as a minimal important difference (MID) in treatment effect may also not be specified or substantiated.[28]

Recent analyses suggest such measures need greater standardization and more appropriate use.[29] In a review of 57 RCTs of drugs for dementia,[30] less than half discussed MID, and those that did used opinion-based estimates of MID using different measures of cognitive and global function whose psychometric properties remain uncertain.[31] No trial used formally derived and validated MID. Many of these trials reported "positive" treatment effects that, although statistically significant, did not demonstrate effects that are important to patients.[32,33] In contrast, the few trials that used harder end points, such as rates of death, institutionalization, resource use, and clinical events, showed no treatment effect.[34] Physicians and families considering antidementia drug use should be aware that patient-important benefit has not been convincingly demonstrated. This is even more important if there is evidence of possible drug-induced harm, such as increased risk of syncope.[35]

### Missing Outcome Data

In clinical trials, older patients are more likely than younger patients to be lost to follow-up because of withdrawal as a result of cognitive decline, onset of other symptomatic diseases, or logistic impediments to continued trial participation. Older patients may also find it more difficult to fully adhere to the study protocol. Despite attempts to maximize adherence and follow-up, rates of loss to follow-up may remain as high as 20%.[36] Missing outcome data, especially if unequally distributed between the different arms of a trial, threaten trial validity. In such circumstances, investigators may use statistical methods for imputing missing data. Simple imputation strategies, such as last observation carried forward, are most commonly used and then compared with complete case analyses whereby patients with missing data are excluded. However, simple imputation and complete case analyses are prone to bias unless missing data can be shown to occur at random, unrelated to patient characteristics, symptoms, disease severity, group

assignment, or drug adverse effects. This is rarely, if ever, the case. Multiple imputation is preferred whereby several plausible values for missing variables are imputed to create multiple data sets that are then appropriately combined using statistical software.[37] Reanalyses of data from 2 RCTs[38,39] involving older patients revealed that treatment effects deemed significant on last observation carried forward analysis were greatly attenuated or were rendered nonsignificant when subject to multiple imputation analysis.

## ASSESSMENT OF POTENTIAL HARM

### Measuring Harm in Trials

Because the risk of harm from a new treatment is potentially greater in older patients than in younger ones, trials should be vigilant in identifying adverse effects hypothesized on the basis of pharmacologic (in the case of drugs) and physiologic (for devices and physical therapies) factors. To date, most RCTs devote less care and attention to measurement of adverse effects than to measurement of benefits.[40] Longitudinal population-based studies that monitor adverse effects in real-world practice should supplement reporting of harm outcomes in RCTs. In an inception cohort study[41] of 472 older patients with atrial fibrillation commencing warfarin therapy, the cumulative incidence of major hemorrhage for patients 80 years or older was 13.1 per 100 person-years vs 4.7 for those younger than 80 years ($P=.009$). Increasing age, the first 90 days of warfarin therapy, and an international normalized ratio of 4.0 or greater were associated with increased bleeding risk.[41]

### Considering the Potential for Harm in Patient Groups Excluded From Trials

Results of trials involving younger patients should not be applied indiscriminately to older patients who do not meet trial eligibility criteria without rigorous assessment of potential harms. For example, the Randomized Aldactone Evaluation Study[42] demonstrated reduced mortality with spironolactone administration in patients with congestive heart failure whose average age was 60 years. Cohort studies subsequently revealed an "indication drift," with spironolactone being used in older patients.[43] In Ontario, Canada, a more than 3-fold post–Randomized Aldactone Evaluation Study increase in spironolactone prescribing was observed in patients with congestive heart failure who were, on average, 13 years older than trial patients. This was associated with an almost 4-fold rise in the numbers of hospitalizations and deaths secondary to hyperkalemia,[44] underlying the need for especially close monitoring in patient groups more vulnerable to hyperkalemia.

Similarly, after trials involving younger patients who showed less propensity to gastrointestinal bleeding, the use of cyclooxygenase-2 inhibitor agents increased in the general population, in which most people with arthritis are older than 65 years, resulting in a 10% increase in total hospitalizations due to nonsteroidal drug–induced bleeding.[45] Patients in trials and older patients living in the community are likely to differ in comorbidity, cointerventions, and intensity of monitoring, which, in turn, may alter the balance between risk and benefit when therapies are applied more broadly.[9]

## DETERMINING THE ABSOLUTE LEVELS OF BENEFIT AND HARM IN INDIVIDUAL PATIENTS

### Quantifying Benefit and Harm on the Basis of Clinical Trials

Trial investigators should report treatment effects in relative and absolute terms. Thus, although RRR tends to remain constant, absolute risk reduction in future events conferred by treatment will increase in patients with higher baseline risk. This treatment-related absolute risk reduction then needs to be compared with the absolute risks of treatment-induced harm in deciding the extent of net patient-important benefit.

Absolute risk reduction for an individual patient can be estimated by multiplying the RRR derived from the trial (which can be assumed, in most cases, to be the same irrespective of disease severity) by the patient's absolute disease risk. The latter is calculated using risk prediction rules or scoring systems that include age as a risk variable. For example, tools exist for predicting risk of stroke in patients with nonvalvular atrial fibrillation,[46] carotid artery stenosis,[47] and recent transient ischemic attack.[48] Similarly, tools exist for quantifying absolute level of harm with specific treatments, such as bleeding risk secondary to the use of warfarin[49] or fibrinolytic agents[50] and operative risk associated with cardiac surgery[51] or coronary angioplasty.[52]

Consider the decision to start warfarin therapy in a 78-year-old man with nonvalvular atrial fibrillation who has a history of hypertension, ischemic stroke, diabetes mellitus, renal insufficiency, and gastrointestinal bleeding. His CHADS2 (congestive heart failure, hypertension, age older than 75 years, diabetes mellitus, and previous stroke or transient ischemic attack) score[46] is 4, suggesting a thromboembolic stroke rate of 9.1 per 100 patient-years, which warfarin treatment will reduce by approximately two-thirds. His $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older age [age >75 years], reduced platelet count or function, rebleeding risk, hypertension [uncontrolled], anemia, genetic factors [CYP 2C9 single-nucleotide polymorphisms], excessive fall risk [including neuropsychiatric disease], and stroke) score[49] is 4, suggesting a warfarin-induced bleeding rate of 10.4 per 100 patient-years. Such risk quantification enables patients and physicians to more carefully consider the benefit-risk trade-offs involved in treatment decisions.

### Adjustment for Age-Related Infirmity

In assessing net benefit in individual patients, risk related to specific diseases (disease risk) needs to be integrated with age-related infirmity. As age increases, so does the prevalence of physiologic impairment (frailty), comorbidity, psychological impairment (depression and

isolation), disability (limited activities of daily living), and cognitive impairment. As a consequence of exclusion criteria, age-related infirmity in trial patients may be considerably less than that in community patients.[53] Increasing age combined with chronic disease and disability compete with the disease in question in lowering life expectancy. As a result, the potential benefits of disease-specific treatments in individuals become increasingly smaller in absolute terms or are never realized during the patient's remaining life span.[54]

For example, treating microalbuminuria in diabetic patients takes up to 10 years to achieve reductions in overt nephropathy compared with 2 to 3 years to treat hypertension in preventing cardiovascular events.[15] Simple-to-use prognostic indices that combine age, comorbidity, and functional status can precisely estimate life expectancy against which disease-specific mortality and time to treatment benefit can be compared.[55,56] This approach has been used to determine the minimum elapsed time (or payoff time) at which cumulative benefit exceeds cumulative harm for specific care recommendations in the presence of multiple comorbidities.[57] Disease-specific risk indices may also be helpful in identifying patients with a prognosis of less than 6 months in whom more conservative treatment regimens may be preferable.[58]

### Adjustment for Other Treatment Effect Modifiers

Challenges remain in dealing with more complicated sets of circumstances in which (1) treatments may affect QOL and survival to varying degrees or in different directions; (2) individuals regularly move into and out of states of illness and functional impairment[59]; and (3) multiple medications prescribed for different diseases compromise estimation of the additive benefit from initiating new drugs for newly diagnosed conditions.[60] We await the development of tools that can handle these situations in ways readily translatable to everyday care. In the more simple case in which immediate symptom control is the objective and treatment effects of single drugs are ascertainable and short-lived, n-of-1 trials in which individuals serve as their own controls and participate in randomly sequenced periods of placebo or active drug[61] deserve wider use in older populations.

### Eliciting Patient Values and Preferences

**Empowering Patients.** Physicians must align treatment goals with the values and preferences of older patients, who frequently place more emphasis on QOL, functional status, and independence than on survival or discrete clinical events.[62] Treatment choices must reflect the imposed burdens of treatment, which may be considerable for older patients and are often underappreciated.[63] Many are also limited in their ability to participate in self-care as a result of dementia, depression, or hearing or visual impairment.[64] Most, but not all, older patients[65] want to actively share in therapeutic decisions involving risk-benefit trade-offs. Assistive aids are available that render information about treatment options and potential risks more comprehensible. They engender greater confidence in decisions that often eschew more risky interventions.[66]

For example, in a trial that evaluated a decision aid for older patients with nonvalvular atrial fibrillation, patients demonstrated less decisional conflict and were more likely to choose against taking warfarin compared with those subject to guideline-based medical advice.[67] Similarly, in another study[68] of older patients with atrial fibrillation, less than half who opted for warfarin therapy were actually receiving it, whereas more than half who did not want it were prescribed the drug. Only two-thirds of the whole sample preferred warfarin therapy, whereas close to 80% would have met the guideline criteria for eligibility.

**Limitations of Surrogate Opinions.** Some older patients are unable to engage in decision making owing to severe illness, low health literacy, or cognitive impairment. In such circumstances, and if no advance directives are available, the attending physician or surrogate decision makers must make decisions on the patient's behalf. In up to a third of cases, such opinions are at odds with what patients themselves would have preferred.[69] In particular, older patients, even those with fair health, seem much less willing to forego as much a decrease in life span in exchange for excellent health as surrogates assume.[70] Consensus-based approaches that reconcile what is incontestable about patient preferences with the advice of physicians and caregivers lessen the risk of ill-informed surrogate opinions taking undue precedence in end-of-life decisions.[71]

**Prioritizing Therapeutic Goals and Selection of Treatments.** *Minimizing the Risks of Polypharmacy.* Because the risk of harm in older patients increases in proportion to the number of treatments prescribed,[72] it is necessary to prioritize therapeutic goals and selection of treatments. This may run counter to recommendations of current disease-specific, evidence-based guidelines endorsed by specialty societies. For example, in a cohort of older patients hospitalized with heart failure and prescribed guideline-based care from a specialist heart failure team, the average number of cardiac drugs per patient rose from 5.0 on admission to 6.6 at discharge, associated with a 60% increase in the number of potential drug-drug interactions per patient (from 5.0 to 8.0).[73] In a hypothetical 79-year-old woman with 5 chronic diseases described by Boyd et al,[13] guideline-concordant care, if rigorously applied, would mandate 12 medicines requiring 19 doses per day taken up to 5 times during a typical day, with the potential for more than 20 drug-disease, drug-drug, and drug-diet interactions.

*Defining Care Goals and Prioritizing Treatments.* How physicians prioritize recommended treatments has received little study. The evidence that does exist suggests that high-impact treatments tend to be underrated,[74] that more attention is given to long-term rather than short-term treatment goals,[75] and that treatment preferences are sensitive to physician age, training, and practice setting.[76] A construct has been proposed whereby life expectancy, time to realization of treatment benefit, primary goals of care (prevention, cure, or pallia-

tion), and validity of specific treatment targets (such as hemoglobin $A_{1c}$ levels in diabetes mellitus and blood pressure in hypertension) are integrated in determining appropriate treatment for older individuals with the aim of minimizing unwarranted polypharmacy.[77]

Treatment choices need to be prioritized according to the strength of treatment recommendations. Strong recommendations, if appropriately developed, reflect a large gradient between desirable and undesirable patient-important effects and, thus, represent the preferred option for almost all patients. In contrast, weak recommendations indicate greater uncertainty, or a closer balance between desirable and undesirable effects. Increasing use of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system by guideline developers will help physicians and patients discriminate between strong and weak recommendations.[78]

Such an approach is particularly relevant at a time when many guideline recommendations are still based on lower-quality evidence.[79] It may lessen the tension physicians feel between avoiding polypharmacy while still recommending highly effective treatments in eligible patients.[80] In recognition of this tension, some specialty societies are now producing guidelines specific to older populations that incorporate considerations of general health, comorbidities, cognitive status, and life expectancy.[81,82] As a practical application, in a controlled trial[83] that used a drug-discontinuation algorithm centered on an evidence-based consensus around indications and net benefit, 332 different drugs were discontinued in 119 older disabled patients (an average of 2.8 drugs per patient). This resulted in significant decreases in 12-month mortality (21% vs 45%), referrals to acute care facilities (12% vs 30%), and drug costs (decrease of 46¢ in average daily drug cost per patient).

*Assisting Patients in Adhering to Agreed Therapeutic Regimens.* In older patients, physical frailty, forgetfulness, heightened sensitivity to even mild adverse effects, and demands of everyday life may result in nonadherence rates as high as 84%.[84] The more treatments prescribed, the greater the level of nonadherence.[85] Nonadherence is typically underreported by patients and is difficult to predict or detect.[86] In a review of 8 controlled trials involving older patients,[87] adherence was improved in relative terms by a mean of 11% by means of regularly scheduled patient follow-up visits, multicompartment dose administration aids, pharmacist-mediated medication reviews, and group education. Multidisciplinary chronic disease management programs targeted to high-risk patients, such as those with heart failure, have also been shown to improve adherence and reduce mortality and readmissions, but they are more resource intense.[88]

**Table 4. Strategies for Improving the Evidence Base for Older Patient Care**

| Strategy |
|---|
| More meta-analyses of age-stratified individual patient data obtained from randomized trials that include sizable numbers of older patients |
| More clinical trials (preferably randomized megatrials) specific to older patient populations in which: |
| • Trial populations are representative of community populations |
| • Age-based exclusions and other exclusions that disproportionately reduce enrollment of older patients are eliminated where possible |
| • Nonpharmacologic treatments are given equal weighting to pharmacologic treatments |
| • Multidrug regimens are compared directly with simpler regimens |
| • Assessment of physical, psychological, cognitive, and other outcomes is routinely performed using validated, standardized measurement tools |
| • Benefits and harms are rigorously evaluated and reported in absolute and relative terms |
| • Sample size calculations ensure adequate power for age-stratified analyses |
| • Minimal important difference has been prespecified for trials evaluating treatment effects on patient-reported outcomes |
| • Prespecified subgroup analyses are performed to assess primary outcomes according to age (65-74, 75-84, and ≥85 y), treatment intensity or duration of follow-up, and selected comorbidities or levels of premorbid function |
| More observational studies and clinical registries specific to older patients in which: |
| • Outcome measures are standardized and regularly include measures of physical, psychological, and cognitive function |
| • Subgroup analyses are performed if possible as described previously herein |
| • Multivariate regression models are applied to whole cohorts and subgroups in identifying patient types who are more likely to benefit (or be harmed) by treatments in question |
| More clinical practice guidelines that, regarding older patients: |
| • Use the GRADE system or a similar approach that makes explicit recommendations for which there is compelling evidence of benefits substantially outweighing harm under most circumstances |
| • Consider the limitations of applying multiple treatments to patients with multiple chronic diseases |

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

## CONCLUDING COMMENTS

Irrespective of the patient's age, potentially relevant research needs to be critically appraised regarding validity, impact, and applicability; and this research needs to be presented to the clinical end-user in a preprocessed form that is readily interpretable. Physicians who care for older patients need to be adept at seeking out such evidence.[89] Because of the greater risk of harm and the lesser potential for benefit in older patients and the greater variability in treatment effects, the quality of evidence supporting substantial benefit and limited harm needs to be more stringent in older vs younger populations. Administering treatments in older patients, either empirically based on the presumed pathogenesis of the target disease or on the basis of limited evidence, may not be in their best interests. Physicians need to carefully consider their sources of evidence and recommendations[90] and to find the right balance between avoiding the "risk-treatment paradox"—high-risk older patients being denied safe medications capable of materially improving survival or QOL[91]—while avoiding inappropriate use of medications in which risks are likely to outweigh benefit.[92] Clinical decision making should be informed, as much as possible, by the best available evidence. Where evidence is lacking, academic physicians can assist in filling the gaps by advocating the strategies outlined in **Table 4**.[93]

**Accepted for Publication:** November 30, 2009.

**Correspondence:** Ian A. Scott, MBBS, FRACP, MHA, MEd, Department of Internal Medicine and Clinical Epidemiology, Princess Alexandra Hospital, Level 5A, Ipswich Road, Brisbane, Queensland 4102, Australia (ian_scott@health.qld.gov.au).
**Author Contributions:** *Study concept and design:* Scott. *Acquisition of data:* Scott. *Analysis and interpretation of data:* Scott and Guyatt. *Drafting of the manuscript:* Scott. *Critical revision of the manuscript for important intellectual content:* Scott and Guyatt. *Statistical analysis:* Scott and Guyatt. *Study supervision:* Guyatt.
**Financial Disclosure:** None reported.

## REFERENCES

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312(7023):71-72.
2. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med*. 2002;162(15):1682-1688.
3. Hilmer SN, McLachlan A, Le Couteur DG. Clinical pharmacology in geriatric patients. *Fundam Clin Pharmacol*. 2007;21(3):217-230.
4. Kennerfalk A, Ruigomez A, Wallander MA, Wilhelmsen L, Johansson S. Geriatric drug therapy and healthcare utilisation in the United Kingdom. *Ann Pharmacother*. 2002;36(5):797-803.
5. McMurdo MET, Witham MD, Gillespie ND. Including older people in clinical research. *BMJ*. 2005;331(7524):1036-1037.
6. Van Spall HGC, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA*. 2007;297(11):1233-1240.
7. Witham MD, McMurdo MET. How to get older people included in clinical studies. *Drugs Aging*. 2007;24(3):187-196.
8. Strandberg T. Does evidence-based medicine do more harm than good for the elderly? *Evid Based Cardiovasc Med*. 2004;8(2):115-116.
9. Le Couteur DG, Kendig H. Pharmaco-epistemology for the prescribing geriatrician. *Australas J Ageing*. 2008;27(1):3-7.
10. Studenski S. Challenges in clinical aging research: building the evidence base for care of the older adult. *J Am Geriatr Soc*. 2008;56(12):2351-2352.
11. Nelson EA, Dannefer D. Aged heterogeneity: fact or fiction? the fate of diversity in gerontological research. *Gerontologist*. 1992;32(1):17-23.
12. O'Hare AM, Kaufman JS, Covinsky KE, Landefeld CS, McFarland LV, Larson EB. Current guidelines for using angiotensin-converting enzyme inhibitors and angiotensin II-receptor antagonists in chronic kidney disease: is the evidence base relevant to older adults? *Ann Intern Med*. 2009;150(10):717-724.
13. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005;294(6):716-724.
14. Tinetti ME, Bogardus ST Jr, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med*. 2004;351(27):2870-2874.
15. Glasziou P, Guyatt GH, Dans AL, et al. Applying the results of trials and systematic reviews to individual patients. *Evidence-based Med*. 1998;3:165-166.
16. Beckett NS, Peters R, Fletcher AE, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358(18):1887-1898.
17. Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER Study Group (PROspective Study of Pravastatin in the Elderly at Risk). Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360(9346):1623-1630.
18. Keime-Guibert F, Chinot O, Taillandier L, et al; Association of French-Speaking Neuro-Oncologists. Radiotherapy for glioblastoma in the elderly. *N Engl J Med*. 2007;356(15):1527-1535.
19. Strandberg TE, Pitkala KH, Berglind S, Nieminen MS, Tilvis RS. Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: the Drugs and Evidence-based Medicine in the Elderly (DEBATE) study: a randomised, controlled trial. *Am Heart J*. 2006;152(3):585-592.
20. Fletcher AE, Price GM, Ng ESW, et al. Population-based multidimensional assessment of older people in UK general practice: a cluster-randomised factorial trial. *Lancet*. 2004;364(9446):1667-1677.
21. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. *Drugs Aging*. 2008;25(12):1021-1031.
22. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet*. 2009;373(9670):1190-1197.
23. Pignon J-P, le Maitre A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. 2009;92(1):4-14.
24. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494-502.
25. Guyatt G, Wyer P, Ioannidis JPA. When to believe a subgroup analysis. In: Guyatt G, Rennie D, Meade MO, Cook DJ, eds. *Users' Guides to the Medical Literature: A Manual for Evidence-based Clinical Practice*. 2nd ed. Toronto, Ontario, Canada: McGraw-Hill; 2008:571-593.
26. Setoguchi S, Glynn RJ, Avorn J, Mittleman MA, Levin R, Winkelmayer WC. Improvements in long term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge. *J Am Coll Cardiol*. 2008;51(13):1247-1254.
27. Skolnick AH, Alexander KP, Chen AY, et al. Characteristics, management, and outcomes of 5,557 patients age > or =90 years with acute coronary syndromes: results from the CRUSADE Initiative. *J Am Coll Cardiol*. 2007;49(17):1790-1797.
28. Wyrwich KW, Bullinger M, Aaronson N, Hays RD, Patrick DL, Symonds T; Clinical Significance Consensus Meeting Group. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res*. 2005;14(2):285-295.
29. Contopoulos-Ioannidis DG, Karvouni A, Kouri I, Ioannidis JPA. Reporting and interpretation of SF-36 outcomes in randomized trials: systematic review. *BMJ*. 2009;338:a3006.
30. Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance employed in randomized controlled trials of drugs for dementia. *J Am Geriatr Soc*. 2009;57(3):536-546.
31. Banerjee S, Samsi K, Petrie CD, et al. What do we know about quality of life in dementia? a review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia. *Int J Geriatr Psychiatry*. 2009;24(1):15-24.
32. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med*. 2008;148(5):379-397.
33. Burns A, Bernabei R, Bullock R, et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. *Lancet Neurol*. 2009;8(1):39-47.
34. Courtney C, Farrell D, Gray R, et al; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomized double-blind trial. *Lancet*. 2004;363(9427):2105-2115.
35. Gill SS, Anderson GM, Fischer HD, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. *Arch Intern Med*. 2009;169(9):867-873.
36. Macias FM, Ramsay RE, Rowan AJ. Recruitment and retention in clinical trials of the elderly. *Int Rev Neurobiol*. 2007;81:265-272.
37. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
38. Houck PR, Mazumdar S, Koru-Sengul T, et al. Estimating treatment effects from longitudinal clinical trial data with missing values: comparative analyses using different methods. *Psychiatry Res*. 2004;129(2):209-215.
39. Fielding S, Fayers PM, McDonald A, McPherson G, Campbell MK; RECORD Study Group. Simple imputation methods were inadequate for missing not at random (MNAR) quality of life data. *Health Qual Life Outcomes*. 2008;6:57-62.
40. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA*. 2001;285(4):437-443.
41. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115(21):2689-2696.
42. Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709-717.
43. Bozkurt B, Agoston I, Knowlton AA. Complications of inappropriate use of spironolactone in heart failure: when an old medicine spirals out of new guidelines. *J Am Coll Cardiol*. 2003;41(2):211-214.
44. Juurlink DN, Mamdani MM, Lee DS, et al. Rates

of hyperkalaemia after publication of the Randomised Aldactone Evaluation Study. *N Engl J Med*. 2004;351(6):543-551.
45. Mamdani M, Juurlink DN, Kopp A, Naglie G, Austin PC, Laupacis A. Gastrointestinal bleeding after the introduction of COX 2 inhibitors: ecological study. *BMJ*. 2004;328(7453):1415-1416.
46. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. *Am Heart J*. 2008;156(1):57-64.
47. Barnett HJ, Taylor DW, Eliasziw M, et al; North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med*. 1998;339(20):1415-1425.
48. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369(9558):283-292.
49. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151(3):713-719.
50. 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(2):119-129.
51. Nashef SAM, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16(1):9-13.
52. Qureshi MA, Safian RD, Grines CL, et al. Simplified scoring system for predicting mortality after percutaneous coronary intervention. *J Am Coll Cardiol*. 2003;42(11):1890-1895.
53. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. *JAMA*. 2007;298(10):1209-1212.
54. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. *Br J Cancer*. 2004;91(7):1229-1235.
55. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA*. 2006;295(7):801-808.
56. Welch HG, Albertsen PC, Nease RF, Bubolz TA, Wasson JH. Estimating treatment benefits for the elderly: the effect of competing risks. *Ann Intern Med*. 1996;124(6):577-584.
57. Braithwaite RS, Concato J, Chang CC, Roberts MS, Justice AC. A framework for tailoring clinical guidelines to comorbidity at the point of care. *Arch Intern Med*. 2007;167(21):2361-2365.
58. Huynh BC, Rovner A, Rich MW. Identification of older patients with heart failure who may be candidates for hospice care: development of a simple four-item risk score. *J Am Geriatr Soc*. 2008;56(6):1111-1115.
59. Hardy SE, Gill TM. Recovery from disability among community-dwelling older persons. *JAMA*. 2004;291(13):1596-1602.
60. Saver JL, Kalafut M. Combination therapies and the theoretical limits of evidence-based medicine. *Neuroepidemiology*. 2001;20(2):57-64.
61. Guyatt G, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy: randomised trials in individual patients. *N Engl J Med*. 1986;314(14):889-892.
62. Bradley EH, Bogardus ST Jr, Tinetti ME, Inouye SK. Goal-setting in clinical medicine. *Soc Sci Med*. 1999;49(2):267-278.
63. May C, Montori VM, Mair FS. We need minimally disruptive medicine. *BMJ*. 2009;339:b2803.
64. Brauner DJ, Muir JC, Sachs GA. Treating nondementia illnesses in patients with dementia. *JAMA*. 2000;283(24):3230-3235.
65. Levinson W, Kao A, Kuby A, Thisted RA. Not all patients want to participate in decision-making: a national study of public preferences. *J Gen Intern Med*. 2005;20(6):531-535.
66. O'Connor AM, Bennett CL, Stacey D, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2009;(3):CD001431.
67. Thomson RG, Eccles MP, Steen IN, et al. A patient decision aid to support shared decision-making on anti-thrombotic treatment of patients with atrial fibrillation: randomized controlled trial. *Qual Saf Health Care*. 2007;16(3):216-223.
68. Protheroe J, Fahey T, Montgomery AA, Peters TJ. The impact of patients' preferences on the treatment of atrial fibrillation: observational study of patient based decision analysis. *BMJ*. 2000;320(7246):1380-1384.
69. Shalowitz DI, Garrett-Mayer E, Wendler D. The accuracy of surrogate decision makers: a systematic review. *Arch Intern Med*. 2006;166(5):493-497.
70. Tsevat J, Dawson NV, Wu AW, et al; HELP Investigators. Health values of hospitalized patients 80 years or older: Hospitalized Elderly Longitudinal Project. *JAMA*. 1998;279(5):371-375.
71. Karlawish JHT, Quill T, Meier DE; ACP-ASIM End-of-Life Care Consensus Panel. A consensus-based approach to providing palliative care to patients who lack decision-making capacity. *Ann Intern Med*. 1999;130(10):835-840.
72. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348(16):1556-1564.
73. Ledwidge M, Travers B, Ryder M, Ryan E, McDonald K. Specialist care of heart failure improves appropriate pharmacotherapy at the expense of greater polypharmacy and drug-interactions. *Eur J Heart Fail*. 2004;6(2):235-243.
74. Hofer TP, Zemencuk JK, Hayward RA. When there is too much to do: how practising physicians prioritize among recommended interventions. *J Gen Intern Med*. 2004;19(6):646-653.
75. Rakow T. Differences in belief about likely outcomes account for differences in doctors' treatment preferences: but what accounts for the differences in belief? *Qual Health Care*. 2001;10(suppl 1):i44-i49.
76. Stange KC, Fedirko T, Zyzanski SJ, Jaen CR. How do family physicians prioritise delivery of multiple preventive services? *J Fam Pract*. 1994;38(3):231-237.
77. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med*. 2006;166(6):605-609.
78. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
79. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301(8):831-841.
80. Avezum A, Makdisse M, Spencer F, et al; GRACE Investigators. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J*. 2005;149(1):67-73.
81. Alexander KP, Newby K, Cannon CP, et al; American Heart Association Council on Clinical Cardiology; Society of Geriatric Cardiology. Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation*. 2007;115(19):2549-2569.
82. Alexander KP, Newby LK, Armstrong PW, et al; American Heart Association Council on Clinical Cardiology; Society of Geriatric Cardiology. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation*. 2007;115(19):2570-2589.
83. Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. *Isr Med Assoc J*. 2007;9(6):430-434.
84. Al-Rashed SA, Wright DJ, Roebuck N, Sunter W, Chrystyn H. The value of inpatient pharmaceutical counseling to elderly patients prior to discharge. *Br J Clin Pharmacol*. 2002;54(6):657-664.
85. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials on interventions to assist patients to follow prescriptions for medications. *Lancet*. 1996;348(9024):383-386.
86. McElnay JC, McCallion CR, al-Deagi F, Scott M. Self-reported medication non-compliance in the elderly. *Eur J Clin Pharmacol*. 1997;53(3-4):171-178.
87. George J, Elliott RA, Stewart DC. A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications. *Drugs Aging*. 2008;25(4):307-324.
88. McAlister FA, Stewart S, Ferrua S, McMurray JV. Multidisciplinary strategies for the management of heart failure patients at high risk for admission. *J Am Coll Cardiol*. 2004;44(4):810-819.
89. Guyatt GH, Meade MO, Jaeschke RZ, Cook DJ, Haynes RB. Practitioners of evidence based care: not all clinicians need to appraise evidence from scratch but all need some skills. *BMJ*. 2000;320(7240):954-955.
90. Spinewine A, Swine C, Dhillon S, et al. Appropriateness of use of medicines in elderly inpatients: qualitative study. *BMJ*. 2005;331(7522):935-939.
91. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA*. 2004;291(15):1864-1870.
92. Aparasu RR, Mort JR. Inappropriate prescribing for the elderly: Beers criteria based review. *Ann Pharmacother*. 2000;34(3):338-346.
93. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. 2003;290(12):1624-1632.

ined the question of whether the albumin to creatinine ratio (ACR) can help in risk stratification in elderly patients with diabetes mellitus and with varying levels of eGFR.[11] They reported that over half of the patients 75 years or older had CKD, similar to prior reports. Although in younger age groups, the association between ACR and death was stronger among patients with relatively preserved eGFR and attenuated at lower eGFR, the ACR was independently associated with an increased risk of death at all levels of eGFR among patients 75 years or older. Thus, ACR may be a valuable tool for mortality risk stratification in elderly patients, particularly among the large group who meet the criteria for CKD owing to a moderate reduction in eGFR. Given that proteinuria is also a risk factor for progression to ESRD in most populations, it would be informative to determine whether this parameter helps to distinguish between the competing risks of death and ESRD in the population of elderly patients with CKD.

Although this study addresses some of the issues related to interpretation of CKD among elderly patients, many uncertainties still remain. What we can conclude, on the basis of the studies in this issue of *Archives* and others, is that CKD in elderly individuals has clinical implications beyond ESRD, at least when the eGFR is below 45 mL/min/1.73 $m^2$ or is accompanied by proteinuria. In elderly patients, we may need to focus on prevention of mortality and improvement in quality of life as much as, or more than, on prevention of progression to ESRD. Fortunately, these goals often are not mutually exclusive.

*Kirsten L. Johansen, MD*

**Author Affiliation:** Nephrology Section, San Francisco VA Medical Center and Department of Medicine, University of California, San Francisco.
**Correspondence:** Dr Johansen, San Francisco VA Medical Center, 4150 Clement St, PO Box 111J, San Francisco, CA 94121 (kirsten.johansen@ucsf.edu).
**Financial Disclosure:** Dr Johansen receives funding from Abbott Laboratories and Amgen Inc.
**Funding/Support:** Dr Johansen is funded by the San Francisco Veterans Affairs Medical Center and receives research support from the National Institute of Diabetes and Digestive and Kidney Diseases, and the University of California, San Francisco.
**Role of the Sponsors:** The funding sources had no role in the preparation, review, or approval of this editorial.
**Disclaimer:** The views expressed in this article are those of the author and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the University of California.

## REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002; 39(2)(suppl 1):S1-S266.
2. Levey AS, Beto J, Coronado B, et al; National Kidney Foundation Task Force on Cardiovascular Disease. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? what do we need to learn? where do we go from here? *Am J Kidney Dis*. 1998;32(5):853-906.
3. Sarnak MJ, Levey A, Schoolwerth A, et al; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascualr Disease, High Blood Pressure Research, Clinical Cardiology and Epidemiology and Prevention. *Circulation*. 2003; 108(17):2154-2169.
4. Levey AS, Bosch J, Lewis J, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130(6):461-470.
5. Glassock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol*. 2008;3(5):1563-1568.
6. Melamed ML, Bauer C, Hostetter T. eGFR: is it ready for early identification of CKD? *Clin J Am Soc Nephrol*. 2008;3(5):1569-1572.
7. Coresh J, Astor B, Greene T, Eknoyan G, Levey A. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003;41(1): 1-12.
8. Coresh J, Selvin E, Stevens L, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-2047.
9. Lindeman RD, Tobin J, Shock N. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc*. 1985;33(4):278-285.
10. O'Hare AM, Choi A, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. 2007;18(10):2758-2765.
11. O'Hare AM, Hailpern SM, Pavkov EM, et al. Prognostic implications of the urinary albumin-to-creatinine ratio in veterans of different ages with diabetes. *Arch Intern Med*. 2010;170(11):930-936.
12. O'Hare AM, Bertenthal D, Covinsky K, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? *J Am Soc Nephrol*. 2006;17(3):846-853.
13. Raymond NT, Zehnder D, Smith SC, Stinson JA, Lehnert H, Higgins RM. Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. *Nephrol Dial Transplant*. 2007;22(11):3214-3220.
14. Manjunath G, Tighiouart H, Coresh J, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int*. 2003;63(3):1121-1129.

## *Correction*

**Incorrect Sources Cited in Table 3.** In the Special Article titled "Cautionary Tales in the Interpretation of Clinical Studies Involving Older Persons" by Scott and Guyatt, published in the April 12th issue of the *Archives* (2010; 170[7]:587-595), the 3 sources cited in Table 3 on page 590 were incorrect. The sources should have read as follows, reading from the top to the bottom in the Source column: Hlatky et al,[22] 2009; Pignon et al,[23] 2009; and Yusuf et al,[24] 2001, respectively. The rest of the information is accurate.