Cardiovascular disease and the elderly: can the evidence base avoid irrelevance?

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This editorial refers to 'Effect of long-term ACE-inhibitor therapy in elderly vascular disease patients'† by M. Gianni et al., on page 1382

Cardiovascular disease (CVD) in the elderly is a problem of rapidly growing importance. The prevalence in CVD in older persons is currently about three-fold that in younger populations.1 Further, with the disproportionate growth of the elderly population worldwide, the numbers of older patients with CVD will expand considerably. Also contributing to the impact of CVD in the elderly is the sharp increase in the risk of adverse CVD outcomes that occurs with increasing age.2 Finally, the greater comorbidity associated with older age contributes to a more complex CVD patient population.3,4

This confluence of factors creates an increasingly urgent need to understand effective strategies to ameliorate the burden of CVD in older persons.

Historically, however, clinical trials in CVD have focused on young populations and those without substantial comorbidity. The limited enrolment of elderly patients is likely due to several factors, such as concerns about follow-up or competing risks, both of which may threaten trials' internal validity or power. However, the failure to include adequate numbers of older patients represents a serious threat to the external validity of trials. For example, among US Medicare beneficiaries hospitalized with heart failure, <25% of patients met the enrolment criteria for the landmark clinical trials that established the efficacy of ACE-inhibitors, beta-blockers, and aldosterone antagonists.5 Thus, in many cases, clinicians face the increasing problem of providing care for patient populations for which the evidence base is either rudimentary or non-existent.

The analysis by Gianni et al.6 is an important initial step towards filling in the substantial deficiencies in the existing evidence base addressing the burden of CVD in the elderly. This substudy of the HOPE trial evaluated the effects of ramipril on preventing major vascular events in the subgroup of 2755 patients with or at high risk for vascular disease who were over the age of 70. Ramipril was effective in reducing major vascular events in the elderly subgroup. Furthermore, similar relative reductions in risk were observed in subgroups age 70–74, 75–79, and >80 years. Also importantly, in this population that had undergone a successful run-in period, ramipril was safe and relatively well tolerated in older patients.

As the authors point out, focus on the relative benefits of ramipril alone obscures the important finding that older patients accrued substantially larger absolute benefits from treatment because of their higher baseline risk. Because the absolute risk reduction in the primary composite endpoint among patients over 70 was 5.4% compared with 3% in younger patients, the corresponding number needed to treat (NNT) with ramipril to prevent one cardiovascular event in older patients was nearly half as small as that for younger patients. Indeed, the remarkably favourable NNTs in the older population to prevent the individual outcomes of myocardial infarction (NNT = 28), stroke (NNT = 43), and cardiovascular death (NNT = 27) were all half or less of those for the younger population. As adverse event rates did not differ substantially between younger and older patients, the benefits of therapy were not differentially attenuated by safety risks.

Other studies have also shown that elderly patients often have more to gain from therapy even when the risks of treatment increase considerably with age. Alter et al.2 calculated the relative efficacies required to achieve a constant and clinically meaningful absolute benefit, arbitrarily defined as an NNT of 50, with a hypothetical treatment across different age groups. In a large cohort of patients hospitalized with acute coronary syndromes, the higher baseline risk associated with older age exerted a much greater influence on the NNT than the relative risk reduction conferred by treatment. Similarly, because of the baseline risk in the elderly, the treatment-related complication rate exerted relatively little influence on the net benefits associated with treatment.

Although many factors may contribute to the reluctance to treat elderly patients with or at risk for CVD—including concerns about tolerability of therapy or drug–drug interactions with polypharmacy—deficiencies of the current evidence base are likely important. Increasing age is associated with a decreasing likelihood of receiving therapies, and significant treatment gaps exist even among the limited...
proportion of older patients who are ideal candidates for therapy.\textsuperscript{3,7} Furthermore, among the elderly, treatment tends to be reserved for those with lower risk, a phenomenon appropriately called the ‘treatment-risk paradox.’\textsuperscript{8} In one study, for example, statin prescription for secondary prevention was inversely correlated not only with age, but also with the level of baseline risk, and the effects of age and baseline risk had a synergistic effect on statin-prescribing patterns. Given the increase in underlying risk with age, the disproportionate gaps in therapy for older populations may have particularly important consequences.

A more robust evidence base would play a central role in overcoming therapeutic inertia for the large and growing population of older persons with or at risk for CVD. The study by Gianni et al. is only part of a greater solution. Although the findings of significant benefits in an older population are important, the trial exclusion criteria and the use of a run-in period likely resulted in a study population with few competing risks and a relatively low likelihood of adverse events. Thus, it is not clear whether the population was truly representative of older patients with multiple chronic diseases which create complexities in treatment decisions.\textsuperscript{4} We agree with the authors that more relevant clinical trials should be a priority. Specifically, trials must make concerted attempts to enroll much larger and more representative older populations. Although conducting such trials may be costly and pose many challenges, the PROSPER trial serves as an example that it is possible to conduct a large CVD trial in an exclusively older population.\textsuperscript{9}

Because of the substantial challenges of designing relevant randomized trials to address many questions, we must also look to observational studies to provide insights into the effectiveness and safety of treatments in real-world elderly populations. Although the potential for bias and unmeasured confounding are well-known limitations, observational studies can provide much needed guidance when clinical trial data are lacking. For example, although elderly patients were largely excluded from trials of ACE-inhibitors for the treatment of systolic heart failure, the mortality benefit of these therapies has been found in observational studies of a large community-based cohort of elderly patients,\textsuperscript{10} creating the impetus to provide this important treatment in older heart failure patients.

Although retrospective observational studies are potentially important sources of information, clinical registries have increasing potential to generate timely insights into the effectiveness and safety of therapies in representative populations. Such registries are beginning to gain traction on national and international scales (e.g. the ACC National Cardiovascular Data Registries or GRACE). Although such registries admittedly require substantial resources, those integrated effectively into clinical workflow have the potential to facilitate efficient care while collecting critical data. These efforts represent the next frontier in the generation of knowledge about care in real-world clinical populations; as such, their success is instrumental to maintaining an evidence base with relevance to clinical practice.

Hopefully, the study by Gianni et al. will result in more aggressive CVD prevention with ACE-inhibitors in older persons similar to those enrolled in the HOPE trial. Ultimately, establishing an adequate understanding of how to reduce the inordinate impact of CVD in the elderly will demand the implementation of several approaches, including randomized trials with broader applicability, and rigorous observational studies both from existing databases and robust clinical data registries. Without these advances, clinicians face the threat of making therapeutic decisions for older patients using an evidence base that will be increasingly irrelevant.

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