High-Risk Populations

Introduction

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The study of primary prevention of stroke in the general population is a challenge for several reasons. Sample sizes to provide a sufficient number of events to address hypotheses of interest are usually prohibitively large, mainly because stroke events in the general population over age 45 occur at a rate below 1% annually.\(^1\) For example, to detect a hazard ratio of 1.5 with 90% power for a risk factor that is 10% prevalent would require a study with 711 stroke events.\(^2\) With an incidence rate of less than 1%, this implies that a study would have to accrue more than 71 100 person-years exposure (ie, following 20 000 individuals for more than 3 years). That is, although we think of stroke being unfortunately common, its “low” incidence in the general population makes studies of primary prevention prohibitively large and expensive. This is likely a major contributor to the fact that most NIH-funded intervention trials have focused on secondary stroke prevention, where stroke event rates are many times higher and study sample sizes are many times smaller.

These challenges of primary prevention trials, however, may be more than offset when the rewards of successful primary prevention efforts are considered. For two complementary reasons the public health value of preventing a first stroke is many times greater than prevention of secondary stroke: (1) because the number of people at risk is larger, the absolute number of primary strokes is greater than secondary events, and (2) the impact on reducing disability is much greater because many of the sequella and disabilities from the primary stroke persist even through potential secondary strokes. So the study of primary prevention is a difficult but remarkably valuable endeavor.

This session reviews challenges and opportunities to advance the study of primary prevention of stroke. Perhaps the most direct opportunity is to attempt to “enrich” study populations with individuals at higher risk for incident stroke, and thereby increase event rates and the associated feasibility of studies. Because the risk of stroke more than doubles with each increasing decade of life,\(^3\) perhaps the most straightforward approach to enriching a population for events is to recruit an older cohort.

However, an equally promising approach is to attempt to consider the risk factor profile of potential participants to select a population at higher risk for stroke events. Fortunately, studies such as Framingham\(^4\) and the Cardiovascular Health Study\(^5\) have provided excellent tools for evaluating risk of incident stroke on the basis of “traditional” stroke risk factors. There are at least two major challenges to this approach. First is the decision of how and whether to include “nontraditional” or “emerging” risk factors\(^6\) including new biomarkers of stroke risk into the evaluation of risk. In addition, these risk functions were largely developed in white populations, and may not adequately reflect the underlying forces contributing to the immense racial disparity in stroke risk, particularly that carried by black and Hispanic populations,\(^7, 8\) giving rise to further challenges in the development of approaches to target high-risk populations.

There are also “special” populations where challenges of primary prevention are even greater, with the study of stroke in children and young adults being a prime example. Although the impact of a stroke in this population is striking, so are the challenges of research studies to understand the contributing factors. These challenges introduce the need to consider alternative study designs, such as case/control approaches, which introduce additional study considerations including the impact of a stroke event on risk factor levels that now must be measured subsequent to the occurrence of the stroke event.

All of these considerations culminate and are elucidated in the challenges of designing a primary prevention intervention study. The National Institute of Neurological Disorders and Stroke (NINDS) convened a national workshop to consider what barriers exist and what the potential solutions may be.\(^9\) While these barriers persist, at least one major primary prevention trial in stroke can be considered as showing pathways to addressing these complex issues.\(^10\)

In summary, primary prevention of stroke is a “high risk/high return” area, where barriers are substantial but are perhaps overshadowed by the potential benefits of advances in knowledge. The energy and intellect of the stroke community needs to continue its focus on this challenging and important area for future study.

Disclosures

None.

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