EDITORIAL COMMENT

Adherence to Medical Therapy and the Global Burden of Cardiovascular Disease*

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Ischemic heart disease and cerebrovascular disease account for >20% of worldwide mortality and are the 2 leading causes of death on a global basis [1]. Although mortality from ischemic heart disease is greater than that from stroke worldwide, the mortality from stroke is actually higher than from ischemic heart disease in 39% of countries. For example, mortality from stroke is generally higher than that for ischemic heart disease in China, Africa, and South America. In addition, stroke disability-adjusted life-year loss rates exceed ischemic heart disease-related disability in 32% of countries [2]. Because of this, strategies to prevent stroke are essential to the World Health Organization goal of a 25% reduction in premature mortality from noncommunicable diseases by 2025 [3]. Further evidence of the importance of stroke is its inclusion in the new American College of Cardiology/American Heart Association risk calculator to be used in decision making regarding potential indications for statin therapy in primary prevention [4].

Multiple randomized, controlled trials have demonstrated the efficacy of preventive therapies directed toward the treatment of hypertension and blood cholesterol to prevent stroke and myocardial infarction. Most of the medications needed to achieve these results are now available in generic form, thereby reducing the limitations imposed by cost in many countries with developing economies. These therapies are central to national and international guideline recommendations for the prevention of cardiovascular events. The use of these evidence-based treatment strategies among patients being discharged from the hospital has been increased by quality improvement programs such as the American Heart Association Get With the Guidelines [5]. Yet, adherence to medical therapy to improve cardiovascular outcomes by treatment of hypertension and blood cholesterol in the outpatient setting continues to be incomplete and remains a challenge to all health care systems on a global basis.

In this issue of the *Journal*, a real-world, population-based study from Finland underlines the tragic consequences of nonadherence to statin and antihypertensive therapy [6]. Among 58,266 patients without pre-existing stroke or cardiovascular disease (CVD), the year-by-year adherence to statin and antihypertensive therapy was evaluated using electronic medical and prescription records from the Finnish national registers in from 1995 to 2007. In hypercholesterolemia patients with hypertension fatal stroke was more than 7-fold greater for those who did not adhere to both statin and antihypertensive therapy and significantly increased but at a lower level for those who did not adhere to at least 1 of the 2 therapies. Ischemic strokes were slightly more frequent than hemorrhagic strokes and more than twice as frequent as subarachnoid and other types of stroke. Although the potential danger of nonadherence to statin and antihypertensive therapies for the prevention of stroke has been emphasized, this observational study appears to be the first to provide information and real-world data on the association between nonadherence to statin and antihypertensive therapies and the incidence of fatal stroke. As such, it provides compelling observational evidence that we must increase and focus our efforts on understanding and addressing the various factors associated with nonadherence to evidence-based therapies.

There is currently great interest in how treatment with fixed-dose combination drug therapy, sometimes referred to as polypill, might improve adherence to medical therapies. The regular and consistent use of recommended medical therapies or medications varies inversely with the number of medications prescribed. The more medications recommended, the less likely a patient is to remember to take them. Among older patients in whom cognitive decline may be present, it is not unusual to encounter patients with prescriptions for 10 to 15 pills daily. A Cochrane systematic review of fixed-dose combination therapy for the prevention of CVD included ≥1 medication known to lower blood pressure and at least 1 known to improve the blood lipid profile (7). The review included 9 randomized trials involving 7,047 individuals. Fixed-dose combination drug therapy improved adherence to recommended medications by 33% (range, 26% to 41%) compared with usual care. A study involving 623 participants from Australian general practices at high risk of or with CVD randomized patients to fixed-dose combination therapy that included a statin and ≥1 other medications to lower blood pressure. After 18 months, the group assigned to fixed-dose combination medical therapy had greater adherence to treatment (70% vs. 40%) (8). Evidence from the FOCUS project, which examined a fixed-dose combination drug strategy to improve adherence to evidence-based medications for the prevention of CVD among 2,118 patients, showed improved adherence using fixed-combination drugs. Younger age, depression, and complex drug treatment plans were identified as predictors of low adherence (9).

Nurse case management can also be effective to increase adherence to medical therapy. One of the first such programs, the Stanford MULTIFIT program reported >2 decades ago the effectiveness of a nurse-managed outpatient system to modify behavior and improve adherence to medical therapies (10). This program has been expanded by Kaiser Permanente Northern California for many years. Recently, a nurse-led team-based case management program that includes community health workers reported cost-effective results in managing cardiovascular risk factors by optimizing adherence to healthy lifestyle behaviors and prescribed drugs. The intervention group in this randomized trial had significantly greater reductions in blood pressure and cholesterol than the usual care group (11).

The use of mobile health tools such as text messaging, interactive voice response calls, and other programs associated with cellular phones can also assist patients in improving their adherence to medical therapies. It is estimated that there are >6 billion phone users worldwide, and nearly 75% live in low- and middle-income countries (12). Thus, the application of mobile health technologies has the potential to be especially effective in low- and middle-income countries where 80% of the morbidity and mortality from CVD now occurs. In countries with developing economies, the cost of seeing a physician may be difficult to afford and access to physician may be difficult. The return visit with the health care provider and frequent follow-up, which can enhance adherence to medications to lower blood pressure or cholesterol, may not be available to the majority of patients. Studies of interventions using mobile health tools have been conducted in >30 low- and middle-income countries with results that suggest that they may improve patient adherence and disease outcomes (13). For example, a randomized, controlled trial involving 200 patients in Honduras and Mexico with poorly controlled hypertension found better control of blood pressure among those randomized to interactive voice response using mobile health technology (14).

Patient education is consistently identified as a marker for improved adherence to recommended drug therapy. In this regard, it is important to consider the impact of media on patient education. A recent publication from Denmark on 674,000 individuals 40 years of age and older who began statin therapy during the period 1995 to 2010 examined the association of 1,931 statin-related news stories (110 graded as negative, 1,090 as neutral, and 731 as positive) from Danish newspapers, magazines, radio, television, websites, and news bureau feeds with the discontinuation of statin therapy. Early statin discontinuation increased during the study period from 6% to 18% and was positively associated with negative news stories. Discontinuation of statin therapy was also associated with increased risk of myocardial infarction and death from CVD. The authors suggested a need for further research aimed at protocols designed to improve adherence to statin therapy (15). It is clear that patient education and the information available to patients are a critical component in their adherence to medical therapy and must be included in future efforts to improve adherence. However, the nature of such education should be free of bias, be evidence based as much as possible, and focus on the specific patient needs that will optimize cost-effective outcomes.

The results of the study reported in this issue of the *Journal* demonstrating a > 7-fold increase in fatal stroke among patients nonadherent to statin and antihypertensive therapy given to prevent stroke provide a strong and compelling message that

we must step up efforts in health care systems globally to increase adherence to preventive medical therapies. This will require multiple strategies that can include fixed-dose combination pills, tele-prompting, increased counseling, ongoing involvement by health care professionals such as specialized nurses, and a new awareness of the impact of media-directed educational messages on patient behavior. Without greater efforts to improve adherence by patients to prescribed medications and behavior change, our evidence-based treatments will continue to fall short of their potential sometimes tragically resulting in a fatal stroke.

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