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October 31, 2012

Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. FDA-2012-N-0967

Dear Sir or Madam:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million AHA and ASA volunteers and supporters, we appreciate the opportunity to provide comments on the preliminary list of disease areas for the Agency's new patient-focused drug development initiative.

AHA is pleased that the Food and Drug Administration (FDA) has undertaken this initiative to expand opportunities for patients to provide input during the drug and biologic review process. Patients can provide a unique perspective on the impact of a disease, the severity of the condition, and the adequacy of the existing treatment options. Patients can also provide valuable information on the benefits they'd like a drug to deliver and the acceptable level of risk; two important factors for the Agency to consider as it performs benefit-risk assessments.

As part of this initiative, the FDA is in the process of identifying twenty disease areas that will serve as the topics for future public meetings.

Heart failure is one of the disease areas currently included on the preliminary disease list. We agree that heart failure should be a high priority for this initiative and we urge the FDA to include heart failure on the final list of disease areas. Despite evidence to support a growing number of medication therapies in patients with heart failure over the last several decades, 1 in 5 Americans over the age of 40 will develop the condition in their lifetime.ⁱ Additionally, although many of these therapies have been shown to slow disease state progression and improve overall survival, the mortality rate at 5 years after diagnosis approaches 50%.ⁱⁱ With improved understanding of the etiology and pathophysiology of heart failure, it is now clear that two different types of heart failure exist (although the two may overlap) – heart failure with reduced ejection fraction, where a variety of available therapies exist (although their impact on long-term morbidity, mortality, and quality of life remains limited), and heart failure with preserved ejection fraction, where currently no medication therapies have been shown to improve long-term morbidity and mortality. Irrespective of heart failure type, however, the burden of disease significantly impacts patient quality of life and also serves as a major contributor to health care costs.

In addition, we recommend that FDA add atrial fibrillation, stroke, and peripheral arterial disease to the final list of disease areas. As described below, each of these diseases affects a significant portion of the U.S. population; present symptoms that can affect functioning and activities of daily living; can vary widely in severity; and lack drug therapies that sufficiently address treatment needs.

Atrial Fibrillation

The incidence and prevalence of atrial fibrillation has grown with the aging of the U.S. and world population, with some reports estimating that over 6 million Americans are currently affected by the condition.^{iii,iv} The diagnosis of atrial fibrillation carries a twofold increase in mortality compared to the overall population^v, with the risks approaching tenfold in the first several months immediately following diagnosis.^{vi} Atrial fibrillation also increases the incidence of stroke and hospital admission^{vii,viii} and leads to declines in cognitive function and quality of life.^{ix,x} Despite the significant number of patients impacted by this disease, less than half are thought to be adequately managed and even fewer remain symptom-free.^{xi,xii} Much of this limited efficacy is a result of few therapies being available to safely maintain normal sinus rhythm, as many drugs have been associated with significant toxicities or are contraindicated in patients with comorbid cardiovascular conditions. Safely reducing the risk of stroke and systemic embolism has also remained a challenge given a population that is often at increased risk of bleeding. While the advent of novel oral anticoagulants has provided some promise (as compared to warfarin, the standard bearer for several decades), a number of disadvantages (e.g., adverse effects, lack of reversibility, limited monitoring capabilities when required, dearth of data in patients with renal impairment) are associated with these newer therapies.

Stroke

In addition to being a significant contributor to mortality in the U.S. (one death is estimated to occur every 4 minutes),^{xiii} stroke survivors often face significant mental and physical disability that can affect quality of life and put them at risk for a diverse array of complications. These disabilities, as well as the complications that may result, also represent significant cost, both for patients and their families as well as the overall health care system (i.e., hospitalizations, rehabilitation, assistance for specific disabilities), with estimates exceeding billions of dollars in direct and indirect costs.^{xiv} Despite the broad range of patients impacted by this condition, very few therapies are available for either the acute management of an active stroke or the long-term secondary prevention of recurrent strokes. For those therapies that have demonstrated some impact on clinical outcomes, the long-term benefits are limited and significant advances in the medications used to treat stroke have not been made in well over a decade.

Peripheral Arterial Disease

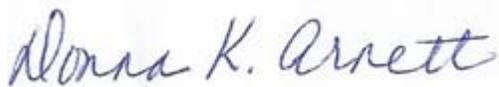
Approximately 8 million Americans are impacted by peripheral arterial disease, and some estimates indicate that up to 1 in 5 individuals over the age of 65 have some form of the condition.^{xv,xvi} The rising incidence of peripheral arterial disease has largely been attributed to increasing rates of diabetes mellitus, although cigarette smoking remains another significant contributor.^{xvii} Although the condition has become increasingly common, less than a third of patients are appropriately managed with the few currently recommended therapies (e.g., antiplatelet and lipid-lowering therapy) that are available.^{xviii} Very few randomized trials exist to support the medication therapy recommended for peripheral vascular disease and even these have only limited impact on the disease state and its often debilitating symptoms.

In closing, we appreciate the FDA's efforts to identify the disease areas that will serve as the focus of this initiative. We understand that this is a difficult task. All disease areas should have expanded opportunities for patient input in the drug and biologic review process; narrowing the list to twenty will be a challenge.

The FDA should, however, keep heart failure as a priority disease area, and strongly consider adding atrial fibrillation, stroke, and peripheral arterial disease to the final list of disease areas. As noted above, our recommendations are based on the prevalence of these conditions in the population, the adverse impact they have on functional ability and quality of life, and the need for additional drug therapies that can effectively address patient symptoms and improve health outcomes. Because heart failure, atrial fibrillation, stroke, and PAD can have a tremendous impact on patients – and cardiovascular disease and stroke remain a leading source of disability and the number one and number four causes of death in the U.S., respectively – we request that FDA ensure that CVD and stroke are well-represented in the patient-focused drug development initiative.

Thank you for consideration of our comments.

Sincerely,



Donna K. Arnett, PhD, BSN
President, American Heart Association

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^{iv} Miyasaka Y, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:e498 and 2006;114:119–125.

^v Stewart et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley Study. *Am J Med* 2002; 113: 359-364.

^{vi} Miyasaka Y, et al. Mortality trends in patients diagnosed with first atrial fibrillation. A 21-year community-based study. *J Am Coll Cardiol* 2007;49:986–992.

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- ^{vii} Go AS. The epidemiology of atrial fibrillation in elderly persons: The tip of the iceberg. *Am J Geriatr Cardiol* 2005; 14:56–61.
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- ^x Reynolds MR, et al. Impact of hospitalization on health-related quality of life in atrial fibrillation patients in Canada and the United States: results from an observational registry. *Am Heart J*. 2010 Oct;160(4):752-8.
- ^{xi} *Record AF registry results (available at <http://www.recordaf.org>).*
- ^{xii} *Realise AF registry results (available at <http://www.realiseaf.org>).*
- ^{xiii} Centers for Disease Control and Prevention. Vital Statistics Public Use Data Files - 2008 Mortality Multiple Cause Files. Available at: http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm#Mortality_Multiple. Accessed September 23, 2011.
- ^{xiv} Medical Expenditure Panel Survey (MEPS) of the Agency for Healthcare Research and Quality (AHRQ). Household component summary data table. Table 4: Total Expenses and Percent Distribution for Selected Conditions by Source of Payment: United States, 2008. http://www.meps.ahrq.gov/mepsweb/data_stats/tables_compendia_hh_interactive.jsp?_SERVICE_MEPSSocket0&_PROGRAM_MEPSPGM.TC.SAS&File_HCFY2008&Table_HCFY2008_CNDXP_D&_Debug_. Accessed November 7, 2011.
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- ^{xvii} Hirsch AT, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines. *Circulation*. 2006;113:e463– e654.
- ^{xviii} Bhatt DL, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295: 180–189.