Secondary prevention: a cost-effective yet underutilized strategy for reducing the stroke burden in resource-limited settings

by

Kathryn Rimmer, BA, BS

DISSERTATION

Presented to the Faculty of the Medical School
The University of Texas Southwestern Medical Center
In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF MEDICINE WITH DISTINCTION IN GLOBAL HEALTH

The University of Texas Southwestern Medical Center
Dallas

Title: Secondary prevention: a cost-effective yet underutilized strategy for reducing the stroke burden in resource-limited settings

Name: Kathryn Rimmer

Background: Over two-thirds of global stroke occur in low- and middle-income countries (LMIC), where the populations are affected on average 15 years younger. Those who survive potentially lose their livelihood and are financially vulnerable to health care expenses. On a national level, stroke DALYs rob the developing economy of its workforce. Cost-effective prevention strategies and interventions could help reduce the stroke burden in LMIC. Primary prevention is considered the top priority, but it necessitates sufficient infrastructure and human resources for successful campaigns. In resource-limited health systems, the population at greatest risk for stroke are likely not receiving regular health maintenance.

Objective: Secondary prevention targets the cohort seeking medical attention for an incident stroke. It is hypothesized to be a more feasible strategy of improving stroke rates in LMIC by reducing recurrence in high-risk populations. The objectives of this study are to compare stroke risk and secondary prevention practices across four different countries of varying income level, and to determine which secondary prevention drug regimen would be optimal for resource-limited settings.

Methods: Current economic and health indicator data were collected from the World Bank and the World Health Organization (WHO) on the United States, France, Vietnam, and Peru. Death and disability-adjusted life-years (DALYs) rates along with risk factor prevalences for each country were accessed from the WHO. Literature reviews on secondary prevention of recurrent stroke and healthcare-utilization in the developing world were conducted on MEDLINE and Pubmed databases using the following key words: stroke, epidemiology, risk factors, stroke burden, secondary prevention, secondary prevention drugs, cost-effectiveness, healthcare-utilization, resource-limited settings, developing world, developing countries, and LMIC. Articles that addressed thesis objectives were selected for review. Additionally, the latest country-specific guidelines for secondary prevention of stroke were retrieved online from the relevant national stroke organizations.

Results: Vietnam experienced the highest death (109) and DALY (729) rates for both genders despite having a young population. Peru has the next highest incidence of death (45.8) and DALYs (385) from stroke. There was a trend of increasing stroke burden with decreasing country GNI per capita among the four countries. Each country had a signature risk factor profile; the United States with raised total cholesterol and obesity; France with hypertension, raised total cholesterol, and smoking; Vietnam with the greatest risk of hypertension and the highest prevalence of smoking among men; and Peru with risk of high BMI. Regarding clinical practice, both the United States and France have an established national guidelines on secondary prevention of stroke. Vietnam recently established its own quality standards based on the Royal College of Physicians' recommendations. Peru does not have its own clinical guidelines for secondary prevention, and adherence to evidence-based recommendations is likely variable among Peruvian neurologists.

Conclusion: In the absence of a health system that can adequately screen and monitor common risk factors in its population, most susceptible patients will go untreated until a cerebrovascular event brings them to medical attention. The opportunity to intervene in the high-risk population is at the moment of incident stroke. Secondary prevention is a cost-effective strategy that can be implemented in the interim while sufficient healthcare capacity develops to maximize primary prevention in the future. LMIC must economize according to the constraints of their resources. Therefore, it would be practical to initiate secondary prevention drug therapy according to the top one or two risk factors in the population.

Secondary prevention: a cost-effective yet underutilized strategy for reducing the stroke burden in resource-limited settings

Introduction

The International Medical Exchange Program (IMEP) is a formal medical and research exchange program between UT Southwestern Medical Center in Dallas, Texas and the Université de Paris, Faculté de Médecine Descartes in Paris, France. Upon completion of required third-year clerkships, participating medical students pursue an additional twelve months of medical curriculum abroad, which allows in-depth global health experiences across three different countries: France for six months, and two other lesser-developed countries for three months each.

Participating in the IMEP was a unique opportunity to gain insight into diverse health systems around the world. I selected Vietnam and Peru as rotation sites for the latter half of the exchange program because of diversity, cultural influences on health-seeking behavior, language, and geopolitical stability. Clinical rotations in France, Vietnam, and Peru allowed me to see how each country manages patients in the context of its local resources and culture. Overall, there were more often similarities between the United States and the three countries with regard to diagnostic capabilities and treatment plans. The greatest differences involved healthcare capacity, technology, infrastructure, and medical training.

Comparison of Health Systems

France

The French health system accomplishes universal health insurance coverage within a mixed setting of public and private health services. There is wide access to comprehensive health services, and the system manages greater resources and a higher utilization of service than the United States (as measured by number of health personnel, hospital beds, and length of hospital stay) [1]. French residents are free to navigate among the public and private options, and the fee-for-service charges are reimbursed by the French national health insurance (NHI). Benefits not covered by French NHI can be purchased through supplementary insurance, to which 90% of the population subscribe [1].

I worked within both the public and private health sectors in Paris. The first IMEP quarter was spent rotating on anesthesia and pain management at three sites: Cochin Hospital, Port Royal Maternity Hospital, and Hôtel-Dieu. These are 3 of the 37 hospitals that form the Assistance Publique – Hôpitaux de Paris (AP-HP) system, which serves as the public hospital network of the Paris region as well as the largest university medical center in Europe [2]. The second IMEP quarter was spent on the neurology service at Saint-Joseph, a private charity hospital in the 14th arrondissement. In general, the quality of care and the inpatient experience were similar to what I had observed as a medical student in the United States' health system. Major differences were related to the benefits of universal health care, the organization of services, and the maintenance of patient records.

Universal health coverage not only encourages patients to see their physician regularly and in acute medical situations, but it allows the physician to focus on the treatment plan and not the patient's ability to pay. Because every patient is covered under the French NHI, insurance status or issues such as a drug not being on prescription formulary were never questions dealt with in France; however, these concerns frequently arise in the United States. Additionally, the extensive pharmaceutical benefits of the French NHI ensure that the prescribed treatments are affordable.

The organizational differences were most apparent in the team and hospital structure. On the neurology service at Saint-Joseph, the physicians, nurses, and therapists held a multidisciplinary meeting every morning to discuss overnight events, patient progress, and discharge planning. This one-hour *staff* took place before patients would be rounded on for the day. The dynamic was collaborative and kept everyone, whether medical student, charge nurse, attending, or physical therapist, updated on service activity. Additionally, every health professional on the service knew each other, and the atmosphere was casual and friendly. That work environment was not unique to Saint-Joseph as I had noticed a similar camaraderie among the hospital staff at Cochin, Port Royal, and Hôtel-Dieu. Contrasting those experiences with rotations at my home institution, there is more apparent hierarchy in the United States. The physicians, nurses, and therapists all work together for patient care; however, multidisciplinary rounds are less frequent, and most communication between health professionals occurs in the electronic medical record or over the phone rather than face-to-face.

Regarding patient records, some hospitals were equipped with an electronic system, but that appeared to be the exception rather than the rule. Where I rotated, all paperwork was kept in a folder or binder, and most documents were handwritten. The hospital maintained most inpatient documents that would incur from an admission; however, patients were given lab results and the actual imaging films along with the discharge summary to keep. At clinic visits, patients were responsible for bringing their personal health records for the physician to review.

Vietnam

In 1954, the government of North Vietnam established a public health system that reached the smallest rural settlements [3]. After reunification in 1976, the health system was extended to the south [3]. For about a decade, health outcomes were strong due to an extensive primary care network and promotion of free access to basic health care as a universal right [4]; however, the government would not be able to sustain it. In the late 1980s, quality of health care began to decline due to budgetary constraints, inadequate staffing, and a shift of responsibility to rural providers [3].

In 1986, the *đổi mới* market-oriented economic reform allowed private investment in public services, and health care in public hospitals became commercialized [4]. By 1989, private medical practice became legal. Though treatment standards have improved, these reforms shifted the fiscal burden of health care onto the individual. Out-of-pocket payments have been rising in the last 20 years, and the Vietnamese government now only subsidizes about 20% of the formal cost [4,5]. Because of an insufficient number of physicians and a shortage of hospital beds, patients and their families end up paying additional informal fees called "envelope payments" to medical staff in order to assure quality of

care and minimize service delays [4]. Corruption of health services is widespread, and as many as 85% of physicians admit to accepting bribes [4].

The government provides national health insurance, which currently covers 68% of the population [4,6]. Enrollment, however, has not translated to effective coverage for the poor [7]. In reality, the system works in favor of the affluent who can afford the out-of-pocket expenses, whereas the poor face greater barriers to access and tend to underutilize services [7]. Those who remain uninsured are a vulnerable population at high risk of poverty if stricken with medical expenses [4].
The Vietnamese Prime Minister and Ministry of Health are committed to reducing hospital overcrowding and reforming the financing of state-owned hospitals [6]. The country plans to have the entire nation insured by 2015, but rising costs and the trend of increasing private and informal payments make this a challenging goal.

The third IMEP quarter took place in Ho Chi Minh City (HCMC), Vietnam, where I rotated on general surgery in the private FV Hospital. It is a modern healthcare facility that was developed by a group of French doctors with the support of the World Bank in the early 2000s. Many Vietnamese physicians working at FV had privileges at multiple hospitals, and those with whom I worked arranged for me to visit two other public hospitals in the city, University Medical Center HCMC and People Hospital 115.

The differences between the private and public sector were striking and mirrored the extreme range of wealth in Vietnamese society. FV Hospital was as well-equipped and staffed as any hospital in the United States or France. The operating rooms were practically identical to those in Paris, even down to the brand of waterless surgical scrub. The hospital had a valet, dining areas, and a gift shop; it juxtaposed modern health care with other commercial services.

My extended Vietnamese relatives who live in HCMC told me that most Vietnamese locals do not go there for treatment. One reason may be location. FV was built in a newer suburb outside the major districts of HCMC, where more affluent families reside. Another reason may be socioeconomic. The perception of my relatives was that FV Hospital serves the wealthy patient population. Perhaps this is true given that the middle class is turning more to the private sector for high-quality care. Those who can afford to will travel overseas for better, more efficient service [8]. Additionally, the Vietnamese government may encourage citizens earning above a set income to seek private care in order to reserve the overloaded public sector for those in poverty [9].

Though I only spent a few hours at each public hospital during the site visits, both did appear to have a larger volume of patients, especially in the emergency department. The University Medical Center HCMC was equipped with a CT scanner and MRI, and it became the fourth stroke center approved for tissue plasminogen activator (tPA) administration in February 2014. People Hospital 115 was one of the original three stroke centers in HCMC. The facilities there appeared outdated, as the neurology service's patients were all kept in one ward with beds lined up side-by-side. All patient charts and documentation were completely handwritten. Families would stay at the patient's bedside and frequently supplemented nursing care. The hospital appeared to function above capacity, as patients and their families overflowed into the hallways.

The public infrastructure does not meet the standards of modern medicine, and the budget of the Ministry of Health is restricted such that a majority of hospitals are outdated and the salaries of health professionals are minimal [10]. According to the Vietnamese Ministry of Health, wait times at public hospitals average 4-7 hours and bed occupancy can be up to 170% [8]. In general, Vietnamese perception of the public hospital system is poor because of the chronic shortages of resources and personnel [8]. As a consequence, the informal envelope payments evolved as an extra expense for patients or their families in addition to the established service fees. Operating without limitation, the envelope payments end up making the public sector as expensive as the private sector, if not more.

In HCMC, I observed some characteristics unique to Vietnamese society that likely alter access to health care. The first and most striking difference is the usage of motorcycles as primary transportation. Two-wheel vehicles dominate traffic, contributing to pollution and gridlock. The only four-wheel vehicles that I recall seeing were taxis; noticeably absent were ambulances. Emergency services exist, but are few in number and slow to dispatch because of the motorcycle traffic.

Another interesting phenomenon was the closure of some public hospitals for *Tết*, or the lunar new year, a national holiday. Most citizens get between one and two weeks of vacation, and it is a widespread belief that the new year washes away bad luck and brings good fortune for a fresh start. Any misfortune that arises around *Tết* is a foreshadowing of bad luck for the rest of the year. The cultural influence is so powerful that the Vietnamese try to avoid falling ill or going to the hospital in the first weeks of the new year. Additionally, elective procedures are sometimes slow to resume after *Tết* because patients delay scheduling until an adequate amount of time has passed. FV Hospital remained open during the holiday period, likely because it is a private facility; however, it was running with only half the number of usual staff members.

Peru

In 2009, the Peruvian government wrote into law the right of its citizens to universal health coverage [11]. Under the law, three insurance schemes were specified in the health system: contributory, semi-contributory, and subsidized, which are differentiated by increasing levels of public funding for health care coverage. Currently, the health system in Peru is fragmented into five entities: the Ministry of Health (MINSA), which provides for the poor and extremely poor population (36%); EsSalud, which provides for the employed population (20%); and the Armed Forces (FFAA), the National Police (PNP) and the private sector, which together provide for 5.5% of the insured population [11,12]. The uninsured remains at 35% of the country population [11]. As a consequence of many non-integrated subsectors, multiple providers of services and insurance plans exist with high overlap and little coordination between them [12].

The fourth IMEP quarter was completed in Lima, Peru at various healthcare settings that gave me a good overview of public, military, and private medicine. I rotated one month on cardiology at Hospital Edgardo Rebagliati (EsSalud), one month on geriatrics at Hospital Naval (FFAA) and Bamboo Senior Health Services clinic (private), and one month on neurology at Rebagliati and Hospital Maria Auxiliadora (MINSA).

Rebagliati is a large public hospital and comprehensive academic medical center. The diagnostic and therapeutic options were comparable to what is available in the United States or France. In fact, Rebagliati reminded me of Parkland in terms of education and clinical excellence, except that patient information was not computerized. Rounds took place outside patient rooms at a rolling cart that held metal patient charts and imaging films. The one computer available for the service was used to print the prescription list for each patient on duplicate paper. All notes were handwritten, and copies of documents were made with carbon-paper. Following-up on lab or imaging studies meant descending nine flights of stairs to go to the respective departments or archives to pick-up the physical results.

The Hospital Naval and Maria Auxiliadora were also good clinical sites; however, the military facility had some outdated wards with numerous hospital beds lined up side-by-side in a long hallway, similar to what was seen in Vietnam. In contrast, the Bamboo clinic had the most modern facility and technology available for its practice. Maria Auxiliadora is only a few decades old, but the facility already appears much older and worn. As in the other public hospitals, the patient records were all handwritten.

After my first month in Peru, the attending physicians in the EsSalud network coordinated a country-wide strike that lasted about 6 weeks. This phenomenon has happened before in the summers of 2013 and 2012 [13], and the objective each year was to secure better doctor reimbursement from the government. During the strike period, only the emergency room stayed open to admit patients, and residents took on additional workload left by attendings. There was still attending supervision in the hospital, but the physician changed daily such that there was little continuity of care on the service. Moreover, ambulatory visits and elective procedures were cancelled. This action disrupted appointments that take months in advance to schedule, and many patients travel extensively from the surrounding region to receive care at Rebagliati. The strike limited Peruvian access to the health system by reducing the number of providers and delaying follow-up appointments. The consequence of that action on patient health outcomes is unknown, and the situation was further extended by the EsSalud nurses, who commenced their own strike after the physician strike ended.

Stroke practices vary by country

A significant portion of my year abroad was dedicated to neurology rotations. I gained an additional 9 weeks of experience on stroke wards before returning to the United States as a rising fourth-year medical student. From my education in the United States and in France, I understand the value of tPA as a treatment for acute ischemic stroke. Since its approval by the FDA in June 1996 [14], it has revolutionized the acute management of stroke patients. Nearly two decades later, the importance of thrombolytic therapy has been repeatedly stressed in my medical curriculum. Some of my first clinical neurology lessons involved evaluating a candidate for tPA via the NIH Stroke Scale, determining if presentation occurred within the therapeutic window, and interpreting neuroimaging for hemorrhagic and/or ischemic patterns.

Upon working in Vietnam and Peru, I discovered that there was less emphasis on the use of tPA. In HCMC, where roughly 8 million people or ~10% of the national population reside, there were only

three stroke centers capable of giving tPA in early 2014. According to local neurologists, most patients do not arrive within the therapeutic window. Poor public awareness of stroke symptoms, financial constraints, poor infrastructure, and limited availability of stroke specialists are obstacles that limit the utilization of thrombolysis therapy in the developing world [15, 16].

Global Burden of Stroke

Stroke is a major cause of morbidity and mortality worldwide, responsible for 5.9 million deaths and 102.2 million disability-adjusted life-years (DALYs) lost in 2012 [17]. Stroke survivorship may come with permanent disability, which includes paralysis, loss of speech, cognitive decline, or blindness. Over two-thirds of global stroke occur in low- and middle-income countries (LMIC) [15, 17], where the populations are affected on average 15 years younger, during the most productive years of life [16]. Those who survive potentially lose their livelihood and are financially vulnerable to health care expenses. On a national level, stroke DALYs rob the developing economy of its workforce [16, 18]. LMIC carry a greater stroke burden [15-19], and those at greatest risk of stroke are least able to afford either its treatment or the devastating sequelae [16]. In resource-limited health systems, tPA is not a practical acute intervention. Until thrombolysis therapy becomes more accessible and affordable, developing countries should invest in more cost-effective prevention strategies and interventions to reduce stroke morbidity and mortality [15, 16, 19].

Prevention strategies and interventions can either target a whole population or focus on high-risk individuals. Population-based strategies attempt to modify risk factors en masse in order to improve the outcome of an entire population. This approach can be very effective, as in the case of Japan where community-based efforts to control blood pressure led to a reduction of stroke rate by over 85% since the 1960s [19, 20]. Some key factors that contributed to Japan's success include universal health care, government-sponsored chronic disease programs, regular health check-ups, and education about restricting dietary salt [20]. This example highlights the necessity of government participation and an established healthcare infrastructure to significantly impact a population's risk over a long period of time.

Primary prevention is considered the top priority for resource allocation [19], but it necessitates sufficient infrastructure and human resources for successful surveillance programs. In resource-limited health systems, the population at greatest risk for stroke are likely unaware of risk factors [15] and not receiving regular health maintenance. In contrast, secondary prevention targets the cohort seeking medical attention for stroke, and it is hypothesized to be a more feasible strategy for improving stroke rates in resource-limited settings by reducing recurrence in high-risk populations. The objectives of this study are to compare stroke risk and secondary prevention practices across four different countries of varying income level, and to determine which secondary prevention drug therapy would be optimal for resource-limited settings.

Methods

Current economic data and health indicator statistics were collected from both the World Bank [5] and the WHO Global Health Observatory Database [21] on the following four countries: United States, France, Vietnam, and Peru. Stroke burden was defined as the incidence of death and DALYs, and the most comprehensive rates for all countries from the same year were found in data published by the WHO, "Disease and injury estimates for 2004 by cause for WHO Member States" [22]. Country-specific prevalence rates for the following risk factors were also retrieved from data readily available from the WHO [21]: raised blood pressure (BP), raised total cholesterol, body mass index (BMI), and smoking.

Literature reviews on secondary prevention of recurrent stroke and healthcare-utilization in the developing world were conducted on MEDLINE and Pubmed databases using the following key words: stroke, epidemiology, risk factors, stroke burden, secondary prevention, secondary prevention drugs, cost-effectiveness, healthcare-utilization, resource-limited settings, developing world, developing countries, and LMIC. Articles that addressed thesis objectives were selected from the search results and reviewed. Additionally, the most current country-specific guidelines for secondary prevention of transient ischemic attack (TIA) or stroke were retrieved online from the relevant national stroke organizations. Pertinent reference articles were included, and publications in French were translated.

Results

Economic status and health expenditure

The World Bank classifies country income level based on gross national income (GNI) per capita, which is calculated according to the *World Data Atlas* method. "As of 1 July 2014, low-income economies are defined as those with a GNI per capita, calculated using the World Bank Atlas method, of $1,045 or less in 2013; middle-income economies are those with a GNI per capita of more than $1,045 but less than $12,746; high-income economies are those with a GNI per capita of $12,746 or more. Lower-middle-income and upper-middle-income economies are separated at a GNI per capita of $4,125" [23].

According to the World Bank classification, the United States and France are considered high-income countries, whereas Vietnam and Peru are classified as lower middle- and upper middle-income countries respectively. Unlike the United States and France, which have maintained high-income classification for many decades, Vietnam and Peru transitioned from low- and lower middle-income levels respectively within the last decade. Though the GNI per capita of these middle-income countries is modest when compared to the high-income countries, both are at an unprecedented high value for its respective populations. Despite the rapid economic growth of Vietnam and Peru in recent years, both countries still have a sizeable proportion of the population living below the national poverty line [5].

Table 1. Country-specific population and health indicator data.

	United States	France	Vietnam	Peru
Population (millions, 2013)[a]	320	64.3	91.7	30.4
Population median age (years, 2013)[a]	37	41	30	27
Population proportion over 60 (%, 2013)[a]	20	24	9.6	9.3
Life expectancy at birth, overall and male / female (years, 2012)[a]	79 76 / 81	83 79 / 85	76 71 / 80	75 75 / 79
Income level classification (2014)[b]	High	High	Lower middle	Upper middle
GNI per capita (in USD, 2013)[b]	$53,470	$43,460	$1,740	$6,270
Health expenditure per capita ($USD, 2012)[b]	$8,895	$4,690	$102	$337
Health expenditure as percent of GNI (%, 2012)[b]	16.6	10.8	5.86	5.37
OOP health expenditure per capita ($USD, 2012)[b]	$987	$348	$50	$120
OOP health expenditure as percent of GNI (%, 2012)[b]	1.85	0.80	2.87	1.91
Poverty headcount ratio at national poverty lines (% of population, 2014)[b]	-----	-----	17.2	23.9
Physicians, 2004+ (per 1,000 people)[b]	2.67	3.74	0.56	-----
Hospital beds, 2006+ (per 1,000 people)[b]	3.1	7.2	2.66	1.5

[a]Global Health Observatory Data. World Health Organization. Available from http://www.who.int/gho/en/.
[b]World Development Indicators, The World Bank. Available from http://data.worldbank.org/.

Table 1 presents the country-specific health expenditure per capita, and there was a trend of increasing health expenditure per capita with increasing GNI per capita. In 2012, the United States spent the most on health in terms of absolute dollars ($8,895) and as a percent of GNI per capita (16.6%). France's health expenditure per capita was $4,690, which is 10.8% of its GNI per capita. Though France is less economically strong as the United States when comparing GNI per capita, the French population reaches an overall life expectancy that is 4 years longer than that of the United States, which is 79 years [21]. Vietnam spends the least on health per capita, a little over $100, yet its population's overall life expectancy is only 3 years shorter than the high-income country spending the most per capita on health.

The out-of-pocket (OOP) health expenditure as a percent of GNI per capita represents the relative financial burden on individual citizens. As economic status decreases among these four countries, the percentage of one's income being paid OOP for health increases[5]. The following values reflect each

country's estimated OOP health expenditure per capita: $987 in the United States, $348 in France, $50 in Vietnam, and $120 in Peru.

The number of physicians and hospital beds per 1,000 population are measures of healthcare capacity, that being human resources and infrastructure respectively. The numbers shown in Table 1 are outdated, but they reveal a general trend of greater healthcare capacity in the high-income countries versus LMIC. France provided the most physicians (3.74/1,000) and hospital beds (7.2/1,000) for its population. Vietnam had the fewest number of physicians (0.56/1,000), but there was no statistic available from Peru to compare between the LMIC. Overall, Peru's infrastructure had the fewest number of hospital beds (1.5/1,000) for its population.

Stroke burden

The most recent available data for both stroke mortality and morbidity (as measured in DALYs) are presented for each country in Table 2. These values are the most comprehensive statistics collected by the WHO [22,24]; however, they are outdated by a decade and may not accurately reflect stroke rates at present. Another limitation of these data is variable accuracy and completeness among national death registries, especially in countries where routine death certificates are not verified by a medical professional [16, 19, 25].

Overall, Vietnam experienced the highest death (109) and DALY (729) rates for both genders despite having a young population (median age 30, see Table 1). Between the sexes, Vietnamese men had a greater risk of stroke morbidity and mortality than Vietnamese women. Peru has the next highest incidence of death (45.8) and DALYs (385) from stroke, and the risk is fairly even between men and women. Similarly, Peru had a younger population (median age 27) than both the high-income countries yet carried a greater stroke burden. In terms of economic status and stroke risk, there was a trend of increasing stroke burden with decreasing country GNI per capita among these four countries. Comparing the high-income countries together, France had slightly better death (27.9) and DALY (242) rates than the United States (30.4 and 327 respectively), perhaps due to greater healthcare capacity. Comparing stroke risk between the sexes, men had a greater rate of both death and DALYs across all four countries.

Risk factor profiles

The five main risk factors for stroke are hypertension, smoking, physical inactivity, diabetes, and atrial fibrillation [19, 26]. Raised BP, cholesterol, and tobacco account for 54%, 15%, and 12% of stroke mortality respectively [27]. According to the WHO, evidence-based and cost-effective secondary prevention interventions, such as tobacco cessation, antihypertensives, antithrombotic therapy, and lipid modifiers, have been shown to reduce recurrent vascular events by 75% [28]. The potential health gains of addressing those behavioral and vascular risk factors are substantial, and for that reason, country-specific prevalence rates for the following risk factors were examined: raised BP, raised total cholesterol, BMI, and smoking.

Table 2. Country-specific stroke mortality and morbidity data.

STROKE BURDEN	United States	France	Vietnam	Peru
Total Deaths (2004)[a,b]	160,112	39,473	62,050	8,298
Death rate per 100,000 population, total (2004)[a]*	30.4	27.9	109	45.8
Death rate per 100,000 population, female (2004)[a]*	29.7	24.8	99.5	44.5
Death rate per 100,000 population, male (2004)[a]*	30.7	31.3	120	47.4
Total DALYs (thousands, 2004)[a]	1,240	221	426	80
DALY rate per 100,000 population, total (2004)[a]*	327	242	728	385
DALY rate per 100,000 population, female (2004)[a]*	322	203	637	381
DALY rate per 100,000 population, male (2004)[a]*	332	285	823	389

[a]Disease and injury country estimates for 2004 by cause for WHO Member States. World Health Organization. Available at http://www.who.int/healthinfo/global_burden_disease/estimates_country/en/.
[b]The WHO Global InfoBase. World Health Organization. Available at https://apps.who.int/infobase/.
*Age-standardized

The data presented in Table 3 are all age-standardized estimates of adult populations from the WHO Global Health Observatory Database [21]. Raised BP was defined as systolic blood pressure (SBP) greater than or equal to 140 mmHg or diastolic blood pressure (DBP) greater than or equal to 90 mmHg or taking an antihypertensive medication. Raised total cholesterol was counted if measured at or above 190 mg/dL. Overweight prevalence was the percent of the population older than 20 years old at or above a BMI of 25 kg/m^2.

The United States' risk factor profile was dominated by raised total cholesterol and obesity; however, Americans had the lowest prevalence of hypertension overall and lower rates of smoking. As presented in Table 3, the United States' prevalence of raised BP was 29.9%, and both sexes had the lowest mean SBP, which were 118 mmHg and 123 mmHg for women and men respectively. Prevalence for raised total cholesterol in adults above 25 years was 53.8%, and slightly more frequent in women. Mean total cholesterol levels for women and men were nearly identical at 197 mg/dL and 193 mg/dL respectively. Smoking prevalence for the population was 19.0%, with men more likely to smoke at 21.6%. Mean BMI was nearly equivalent for women and men at 28.4 kg/m^2 and 28.5 kg/m^2 respectively. The percentage of the population with a BMI at or above 25 kg/m^2 was highest in the United States at 69.4%, and its male population had the highest likelihood of being overweight (72.5%) than any other country population.

Table 3. Country-specific risk factors for stroke.

STROKE RISK FACTORS[a]*	United States	France	Vietnam	Peru
Raised BP, 25+ years old, total (%)	29.9	35.7	36.8	34.3
Raised BP, 25+ years old, female (%)	27.1	29.3	33.7	30.6
Raised BP, 25+ years old, male (%)	32.6	42.3	40.0	38.1
Mean SBP, 25+ years old, female (mmHg, 2009)	118	120	122	120
Mean SBP, 25+ years old, male (mmHg, 2009)	123	131	127	126
Raised total cholesterol, 25+ years old, total (%)	53.8	62.0	36.1	38.6
Raised total cholesterol, 25+ years old, female (%)	54.2	60.2	38.1	39.4
Raised total cholesterol, 25+ years old, male (%)	52.9	63.5	33.9	37.5
Mean Total Cholesterol, 25+ years old, female (mg/dL, 2009)	197	205	182	182
Mean Total Cholesterol, 25+ years old, male (mg/dL, 2009)	193	205	178	182
BMI >= 25 kg/m2, 20+ years, total (%, 2008)	69.4	45.9	10.1	47.9
BMI >= 25 kg/m2, 20+ years, female (%, 2008)	66.3	40.0	10.8	52.2
BMI >= 25 kg/m2, 20+ years, men (%, 2008)	72.5	52.0	9.4	43.3
Mean BMI, 20+ years, female (kg/m2, 2009)	28.4	24.8	21.2	26.1
Mean BMI, 20+ years, male (kg/m2, 2009)	28.5	25.9	21.1	24.9
Current Tobacco Smoking, total (%)	19.0	33.7	23.8	13.3
Current Tobacco Smoking, female (%)	16.5	30.2	1.4	7.8
Current Tobacco Smoking, male (%)	21.6	37.4	47.4	19.7

[a]Global Health Observatory Data. World Health Organization. Available from http://www.who.int/gho/en/.
*Age-standardized

The French risk factor profile was notable for hypertension, raised total cholesterol, and smoking. The raised BP prevalence was 35.7%, and the male population had the highest likelihood of hypertension among the four countries at 42.3%. Additionally, the mean SBP value was highest overall for men at 131 mmHg. Raised total cholesterol prevalence was highest in France at 62%, and both women and men had the highest likelihood of elevated cholesterol among respective sex populations in all four countries. France also had the highest mean total cholesterol values at 205 mg/dL for both women and men. Total smoking prevalence was highest in France at 33.7%, and the likelihood by sex was 30.2% and 37.4% for women and men respectively. Mean BMI was slightly higher in men at 25.9 kg/m^2 as compared to women at 24.8 kg/m^2. The likelihood of being overweight was less than half for the total population; however, the male population had a likelihood of 52%.

The Vietnamese risk factor profile was remarkable for hypertension and male smoking. Raised BP prevalence was highest in Vietnam at 36.8%, and Vietnamese women had the highest risk at 33.7% versus women in the other countries. Mean SBP was 122 mmHg and 127 mmHg for women and men respectively. Raised total cholesterol prevalence was 36.1% for the total population, which is relatively lower than in the high-income countries. Mean total cholesterol values were under 190 mg/dL for both women (182 mg/dL) and men (178 mg/dL). Total smoking prevalence was 23.8%; however, this value is largely skewed by the male rate, which was 47.4%, the highest of any other country population. In contrast, women had a 1.4% likelihood of smoking. The Vietnamese population was least likely to be overweight, with mean BMI values at 21.2 kg/m^2 and 21.1 kg/m^2 for women and men respectively. About 10% of the Vietnamese population had a BMI at or above 25 kg/m^2, and women had a higher likelihood of being overweight (10.8%).

The Peruvian population was at greatest risk of high BMI. Like France and Vietnam, over one-third of the population had hypertension, and men were at increased risk (38.1%) versus women (30.6%). Mean SBP was 120 mmHg and 126 mmHg for women and men respectively. Raised total cholesterol prevalence was 38.6%, which is relatively lower than the high-income countries, but higher than the lower middle-income country, Vietnam. Mean total cholesterol values were below 190 mg/dL for both sexes. The relatively low prevalence of hypertension and raised total cholesterol in the Peruvian population may be explained by its young median age (27 years old, see Table 1). Peruvians were least likely to smoke (13.3%) among all the countries, and the male population had a greater likelihood of smoking (19.7%) than the female population (7.8%). Mean BMI was 26.1 kg/m^2 and 24.9 kg/m^2 for women and men respectively. Nearly half of the Peruvian population was overweight, and women were at higher risk (52.2%) than men (43.3%).

The risk factor trends among the sexes and independent of nationality revealed that men were at greater risk of hypertension, had a higher mean SBP, and were more likely to smoke overall. On the other hand, women were more likely to have raised total cholesterol and a higher mean total cholesterol level than men in all countries except France. In the high-income countries, women were less likely than men to be overweight; however, in the middle-income countries the risk was higher among women.

Clinical guidelines for secondary prevention of TIA or stroke

Evidence-based recommendations provide a consensus for standard of care. It has been shown that implementation of proven medical therapies for secondary prevention of TIA or ischemic stroke is cost-effective [28] and has reduced the recurrence rate of stroke nearly 50% over the past five decades [29].

In the United States, the American Heart Association (AHA) and the American Stroke Association (ASA) dictate the secondary prevention of TIA or stroke guidelines, which are affirmed by the American Academy of Neurology, the American Association of Neurological Surgeons, and Congress of Neurological Surgeons [30]. The latest recommendations were published in July 2014, and those pertaining to medical management are shown in Table 4. Since these secondary prevention guidelines have been released, an article published in *Neurology* has shown that triple class combination of medical therapies (i.e. antihypertensive, antithrombotic, and lipid modifier) for secondary prevention of TIA or ischemic stroke is optimal for reducing recurrence risk of stroke, major vascular events, and all-cause mortality [31].

In France, the Haute Autorité de Santé (HAS), or French National Authority on Health, is responsible for maintaining and updating all national clinical guidelines. The HAS appoints a committee of French neurologists to write the recommendations specific to stroke, and the secondary prevention guidelines are similar to those endorsed in the United States, as shown in Table 4 [32].

Vietnam's Ministry of Health in partnership with the United Kingdom's National Institute for Health and Care Excellence (NICE) recently established its first set of national quality standards for hospital management of acute stroke in July 2014 [33]. Evidence-based recommendations from the Royal College of Physicians' National Clinical Guidelines for Stroke were adapted for implementation into the Vietnamese system [33]. The Vietnamese-specific guidelines are not accessible online; however, those published by the Royal College of Physicians (RCP) are available for review. Assuming that the Vietnamese follow the RCP recommendations as written, the clinical practices are similar to those established by the United States and France.

There are some minor differences among the guidelines, and a side-by-side comparison is displayed in Table 4. First, the RCP has set more stringent BP and cholesterol targets (BP <130/80 mmHg and LDL-C <77 mg/dL respectively) [34]. Additionally, first choice drug recommendations vary for antihypertensive and antiplatelet therapies [30, 32, 34]. For example, the AHA/ASA does not list calcium channel blockers as a recommended antihypertensive drug class [30]; however, both the HAS and the RCP recommend it in addition to diuretics and angiotensin-converting enzyme inhibitors (ACE-Is) [32, 34]. Regarding antiplatelet therapy, the RCP recommends clopidogrel 75 mg daily as the initial choice [34], whereas both the AHA/ASA and HAS endorse aspirin monotherapy [30, 32].

Peru does not have a national set of guidelines to define standard therapy for prevention and treatment of acute stroke. Knowledge of optimal medical therapy for secondary prevention is dependent on training and continuing education, and there is great variability. A resident working in

Table 4. Country-specific guidelines for secondary prevention of TIA or stroke

Indication	United States AHA/ASA[a]	France HAS[b]	Vietnam RCP[c]
Hypertension	SBP >= 140, DBP >= 90	SBP >= 140, DBP >= 90	SBP >= 130, DBP >= 80
	diuretics +/- ACE-I	thiazide or ACE-I or CCB[d]	CCB[d] or thiazide if ethnicity[e] or >55 years, ACE-I or ARB if <55 years
Dyslipidemia	any LDL-C, assume atherosclerotic origin	any LDL-C, assume atherosclerotic origin	TC >154 mg/dL or LDL-C >77 mg/dL
	statin, lifestyle/diet modifications	statin, if >=80 years start at weak dose and titrate	simvastatin 40, use cautiously[f] in ICH
Antiplatelet	noncardioembolic ischemic stroke or TIA	noncardioembolic ischemic stroke or TIA	ischemic stroke or TIA in sinus rhythm
	ASA 50-325 or ASA 25 + dipyridamole 200 ER bid	ASA 75-325 or clopidogrel 75	clopidogrel 75, ASA 75 + dipyridamole 200 ER bid, ASA 75, dipyridamole 200 ER bid
Anticoagulation	nonvalvular AF	nonvalvular AF	valvular or nonvalvular AF
	VKA* or apixaban or dabigatran or rivaroxaban, *INR 2.0-3.0	VKA* or apixaban or dabigatran or rivaroxaban, *INR 2.0-3.0	VKA*, oral non-VKA therapy only if intolerance or allergy, *INR 2.0-3.0
Lifestyle	regular aerobic activity, weight loss if overweight	-----	regular aerobic activity, weight loss if overweight
	diet: low salt, fruits/vegetables, low-fat dairy	-----	diet: low salt, 5 fruits/vegetables daily, 2 oily fish weekly, poly- or monounsaturated fat
	smoking cessation	smoking cessation	smoking cessation
	stop or limit EtOH (men 2 units, women 1 unit daily)	stop or limit EtOH (men 3 units, women 2 units daily)	stop or limit EtOH (men 3 units, women 2 units daily)

[a]Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2014;45:00-00.
[b]Synthèse de la Recommandation de Bonne Pratique: Prévention vasculaire après un infarctus cérébral ou un accident ischémique transitoire. Haute Authorité de Santé, Juillet 2014. www.has-sante.fr.
[c]Intercollegiate Stroke Working Party. National clinical guideline for stroke, 4th edition. London: Royal College of Physicians, 2012.
[d]Dihydropyridine-type
[e]African or Caribbean origin
[f]If required for other indications, otherwise avoid.
TC = total cholesterol, ACE-I = angiotensin-converting enzyme inhibitor; CCB = calcium-channel blocker; ARB = angiotensin-II receptor blocker; ASA = aspirin; AF = atrial fibrillation; VKA = vitamin K antagonist; EtOH = alcohol.

the EsSalud system at the Hospital Edgardo Rebagliati may follow the AHA/ASA recommendations to guide therapy. Similarly, neurologists at the National Institute of Neurological Sciences in Lima, Peru tend to follow AHA/ASA. In contrast, an attending at Hospital Maria Auxiliadora, a public hospital on the outskirts of Lima, would reference España Neurología for clinical guidelines. Both neurologists at Rebagliati and Maria Auxiliadora mentioned that not every Peruvian neurologist follows evidenced-based recommendations, and those practicing in rural communities may have limited continuing medical education.

Discussion

What is optimal medical therapy for secondary prevention of TIA or stroke?
Park and Ovbiagele published the first study that investigated the effect of combinations of individually proven medication classes on future clinical events among stroke patients [31]. The database of a multicenter double-blinded, randomized, controlled trial involving 3,680 recent noncardioembolic stroke patients was analyzed. Patients were categorized according to the number of drugs prescribed divided by the number of drugs potentially indicated. Independent associations of medication appropriateness level with recurrent stroke, major vascular events, and death were assessed. Of the 3,680 study participants across the United States, Canada, and Scotland, 51.0% received optimal therapy (defined as either dual class therapy with antithrombotic (AT) and lipid modifying (LM) drugs if not hypertensive, or triple class therapy with an antihypertensive (AH) in addition to AT and LM drugs).

When compared to no medical therapy, the adjusted hazards ratio for stroke among study patients taking monotherapy or dual class therapy (when triple is indicated) were found to be 0.51 and 0.50 respectively [31]. Triple class therapy had a hazards ratio of 0.39 [31]. For those on monotherapy, the majority of patients were taking AT (n = 355) versus AH (n = 103) and LM (n = 9). Dual class therapy largely included AT in combination with either AH (n = 1,150) or LM (n = 263). Only 69 patients were prescribed AH + LM.

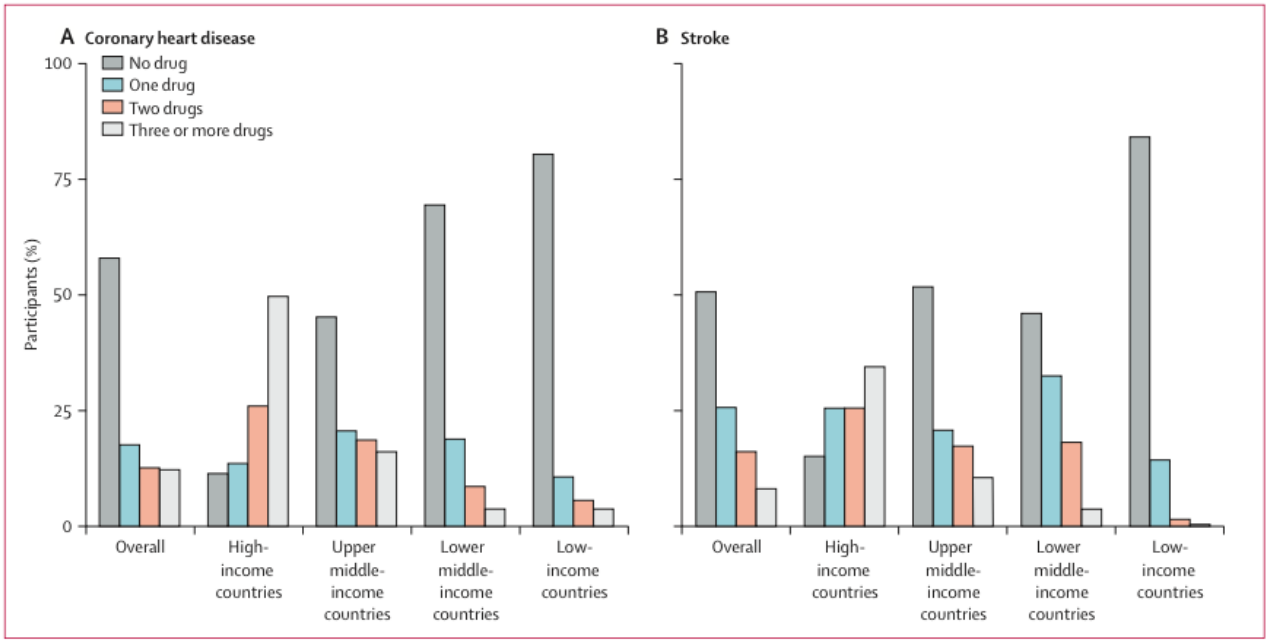
This paper does not directly compare the hazards ratios between monotherapy, dual class, and triple class therapies; however, the data shows that the hazards ratio for monotherapy against no therapy and dual class therapy against no therapy are nearly equivalent. Therefore, the difference between taking one secondary prevention drug versus two drugs may be negligible. Choosing between drug classes ultimately depends on the individual patient's risk factors, but most subjects in the study took AT with or without AH. Despite prevalent hypertension (97.9% of subjects on monotherapy and 80.7% of subjects on dual class therapy or monotherapy if two drugs indicated), the clinical judgement skewed toward treating with AT three times as often as AH, and in dual class therapy, AH was the second drug choice 77.6% of the time.

Effect of country economic status on use of secondary prevention medications

Yusuf et al. have recognized the need for secondary prevention practice data from countries in various stages of economic development, and a prospective epidemiological study (PURE study) was designed to report trends across both urban and rural communities in 17 countries on 5 continents [35]. They found that there was a global underutilization of effective secondary prevention medications [35]. Rate of drug use and the number of drugs taken by individuals declined with decreasing economic wealth [35]. There were strong correlations between overall rates of drug use and per capita health expenditure by country as well as the country's gross domestic product. Two-thirds of the variation in drug use could be accounted for by those country-level factors versus individual-level factors (e.g. age, sex, education, and risk factor profile) [35].

The PURE study revealed there is a definite treatment gap for secondary prevention worldwide, especially in LMIC. It also showed that across all country income levels, about 50% of subjects were receiving treatment, and a majority of those were able to take one or two drugs, see Figure 1. Park's paper showed that greatest net benefit from secondary prevention medication comes from either monotherapy or dual class therapy. Combining these ideas, it is hypothesized that maximizing adherence to one or two secondary prevention drugs has the potential to greatly reduce stroke burden in LMIC [36]. Drug selection should be based on the top country-specific risk factors for maximum benefit. If patient income allows, additional drug classes could be added to the regimen.

Figure 1. Number of drugs taken by individuals by country economic status [35].



For stroke (B), drugs counted were aspirin, statins, ACE inhibitors or ARBs, or other blood-pressure-lowering drugs (eg, β blockers, diuretics, and calcium-channel blockers). ACE = angiotensin-converting enzyme, ARB = angiotensin-receptor blocker.

"Optimized economic" medical therapy for secondary prevention

Each country population has a unique risk factor profile, and knowledge of its tendencies would help formulate a medical therapy plan that suits an individual patient's needs and budget. In the case of Vietnam, where smoking and hypertension were dominant risk factors, antiplatelet monotherapy with aspirin 100 mg daily would be prioritized as the drug intervention, along with smoking cessation, exercise, and a low-salt diet as lifestyle modifications. If dual class therapy became necessary, then an antihypertensive could be added to the regimen. Statin therapy in the Vietnamese population would be a poor choice because raised total cholesterol is less prevalent. In contrast to Vietnam, Peru's main risk factors involved BMI, and to a lesser extent raised total cholesterol. A country-specific treatment plan would first choose antiplatelet monotherapy with diet modification and exercise. If needed, a statin would be the second drug of choice.

Final considerations

The WHO recently published a global status report that defined nine global targets for the prevention and control of noncommunicable diseases (NCDs) by 2025. One of the key messages of the publication is that all countries need to set national targets and establish a monitoring framework to track progress in attaining them [37]. Country-specific policies and interventions that address its own NCD risks and outcomes will allow that particular country to make the best use of its resources [37]. For stroke risk and outcomes, it would be beneficial for the government to fund epidemiology data collection within the public and private sectors. In countries like Peru, where national guidelines for secondary prevention of stroke do not exist, local neurologists should promote cost-effective prevention and treatment guidelines nationwide. Establishing evidence-based recommendations would also allow for standardization of patient care, which is especially valuable in countries where neurologic expertise is lacking.

Conclusion

Patients and physicians face similar health care challenges worldwide, and NCDs are a growing epidemic of the 21st century [37]. Stroke has the same risk factors independent of pre-defined international and cultural borders, and yet LMIC carry most of the stroke burden. Important differences among health systems are related to country economic status and healthcare capacity (i.e. human resources, infrastructure, hospital beds, supplies, etc.). Maturation of a country's health system requires health policy changes and government support [37] that is presumed to occur in stepwise fashion over years if not decades.

In order to effectively improve stroke risk and outcomes in resource-limited settings, prevention needs to be the focus of patient care. However, in the absence of a health system that can adequately screen and monitor common risk factors in its population, most susceptible patients will go untreated until a cerebrovascular event brings them to medical attention. The opportunity to intervene in the high-risk population is at the moment of incident stroke.

Secondary prevention is a proven cost-effective strategy [28, 29, 36] that can be implemented in the interim while sufficient healthcare capacity develops to maximize primary prevention in the future. The WHO recognizes that progress in addressing NCDs remains uneven and inadequate, particularly among LMIC [37]. Until there is worldwide standardization of healthcare, LMIC must economize according to the constraints of their health systems. For this reason, stroke epidemiology needs to be a LMIC priority in order to identify national burden and risk [25]. Reliable stroke data can guide health system planning and monitor the effectiveness of secondary prevention [25]. A targeted strategy of treating the top one or two risk factors in a population may improve adherence to secondary prevention drugs. Since each country has its own risk factor profile, secondary prevention regimens may vary across LMIC.

Completion of this scholarly project has inspired me to pursue future research. First, most LMIC have outdated and/or incomplete stroke epidemiology data, therefore implementation of a low-cost, standardized database for stroke epidemiology and its risk factors would be of great value in LMIC. Additionally, I would like to evaluate recurrent stroke outcomes for patients on strict adherence of either optimal or economic secondary prevention therapy versus no therapy in Vietnam or another LMIC with a heavy stroke burden.

The IMEP experience was a year of broadened perspectives - personally, academically, culturally, and clinically. Seeing the discrepancies of patient care made me realize that factors outside the conventional health sector (e.g. transportation infrastructure, political climate, cultural beliefs, etc.) also influence healthcare delivery and capacity. Working toward equitable and standardized clinical practices worldwide is a worthy goal to which I would like to dedicate myself as a future global neurologist.

References

1. Rodwin VG. The Health Care System Under French National Health Insurance: Lessons for Health Reform in the United States. Am J Public Health. 2003 January; 93(1): 31–37.
2. Assistance Publique-Hopitaux de Paris. Available at http://www.ahap.fr.
3. Country Profile: Vietnam. Library of Congress – Federal Research Division. Available at http://lcweb2.loc.gov/frd/cs/profiles/Vietnam.pdf.
4. Vietnam's healthcare system suffers on policy failure. Oxford Analytica Daily Brief. 27 September 2011.
5. World Development Indicators, World Bank. Available at http://data.worldbank.org/.
6. Vietnam PM seeks improvement of ailing healthcare system. (2013, January 25). Asia News Network. Available at http://www.asianewsnet.net/.
7. Somanathan A, Dao HL, Tien TV. Vietnam - Integrating the poor into universal health coverage in Vietnam. Universal Health Coverage (UNICO) studies series; no.24. Washington, DC: World Bank. January 2013. Available at http://documents.worldbank.org/curated/en/2013/01/17206546/vietnam-integrating-poor-universal-health-coverage-vietnam.
8. Nguyen M. Vietnam Preps for Medical Makeover to Recoup Lost Billions in Healthcare. Reuters. 14 October 2014. Available at http://www.reuters.com/article/2014/10/14/us-vietnam-healthcare-idUSKCN0I32MI20141014.
9. Einhorn B. In Asia, Public Health Care Gets Less Public. Bloomberg Business. 9 September 2010. Available at http://www.bloomberg.com/bw/magazine/content/10_38/b4195014403913.htm.
10. Franco-Vietnamese Hospital : FVH. Geneva Foundation for Medical Education and Research. Available at http://www.gfmer.ch/International_activities_En/FValse_FVH.htm.
11. Seinfield J, Montañez V, Besich N. The Health Insurance System in Peru: Towards a Universal Health Insurance. Global Development Network, March 2013.
12. Peru. Global Health Workforce Alliance. Available at http://www.who.int/workforcealliance/countries/per/en/.
13. Carrillo-Larco R, Taype-Rondán Á, Pereyra-Elías R. Does physicians' right to strike outweigh students' right to an education? The on-going ethical dilemma in Peru. Medical Education Online 2012;17.
14. Practice Advisory: Thrombolytic therapy for acute ischemic stroke – Summary Statement. Neurology 1996;47:835-839.
15. Ghandehari K. Barriers of Thrombolysis Therapy in Developing Countries. Stroke Res Treat 2011;2011.
16. Pandian JD, Padma V, Vijaya P, et al. Stroke and Thrombolysis in Developing Countries. Int J Stroke 2007;2:17-26.
17. Feign VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global burden of Disease Study 2010. Lancet. 2014;383:245-54.

18. Abegunde D, Stanciole A. An estimation of the economic impact of chronic noncommunicable diseases in selected countries. WHO Working Paper. Geneva, Switzerland: World Health Organization Department of Chronic Diseases and Health Promotion, 2006.
19. World Health Organization. Neurological Disorders: Public Health Challenges. Geneva, Switzerland: World Health Organization, 2006. Available at http://www.who.int/mental_health/neurology/neurodiso/en/.
20. World Health Organization. Community-based efforts to reduce blood pressure and stroke in Japan. Geneva, Switzerland: World Health Organization, March 2013. Available at http://www.who.int/features/2013/japan_blood_pressure/en/.
21. World Health Organization. Global Health Observatory Data. Geneva, Switzerland: World Health Organization, 2012. Available at http://www.who.int/gho/en/.
22. World Health Organization. Disease and injury country estimates for 2004 by cause for WHO Member States. Geneva, Switzerland: World Health Organization. Available at http://www.who.int/healthinfo/global_burden_disease/estimates_country/en/.
23. Updated Income Classifications. World Bank. Available at http://data.worldbank.org/news/2015-country-classifications.
24. World Health Organization. The WHO Global InfoBase. Geneva, Switzerland: World Health Organization, 2004. Available at https://apps.who.int/infobase/.
25. Thrift A, Cadilhac D, Thayabaranathan T, et al. Global stroke statistics. Int J Stroke 2014;9(1):6–1.
26. Berkowitz AL, Westover MB, Bianchi MT, Chou SH. Aspirin for secondary prevention after stroke of unknown etiology in resource-limited settings. Neurology 2014;83(11):1004–11.
27. Ezzati M, Vander Hoorn S, Rodgers A, et al. Estimates of global and regional potential health gains from reducing multiple major risk factors. Lancet 2003; 362:271–80.
28. World Health Organization. Prevention of Recurrent Heart Attacks and Strokes in Low and Middle-Income Populations. Evidence-Based Recommendations for Policy Makers and Health Professionals. Geneva, Switzerland: World Health Organization, 2003.
29. Hong K, Yegiaian S, Lee M, et al. Declining Stroke and Vascular Event Recurrence Rates in Secondary Prevention Trials Over the Past 50 Years and Consequences for Current Trial Design. Circulation. 2011;123:2111-2119.
30. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2014;45:00-00.
31. Park J, Ovbiagele B. Optimal combination secondary prevention drug treatment and stroke outcomes. Neurology 2014;84(1):5056.
32. Synthèse de la Recommandation de Bonne Pratique: Prévention vasculaire après un infarctus cérébral ou un accident ischémique transitoire. Haute Authorité de Santé, Juillet 2014. Available at http://www.has-sante.fr.
33. Quality Standard for the Hospital Management of Acute Stroke in Vietnam. July 2014. Available at http://www.nice.org.uk/about/what-we-do/nice-international/nice-international-projects/quality-standard-for-the-hospital-management-of-acute-stroke-in-vietnam.
34. Intercollegiate Stroke Working Party. National clinical guideline for stroke, 4th edition. London: Royal College of Physicians, 2012.

35. Yusuf S, Islam S, Chow C, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet. 2011;378:1231-43.
36. Mendis S. Prevention and care of stroke in low- and middle-income countries; the need for a public health perspective. Int J Stroke 2010;5:86-91.
37. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva, Switzerland: World Health Organization, 2014. Available at http://www.who.int.