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Rebecca W. Persky
University of Connecticut School of Medicine and Dentistry

Lisa Christine Turtzo
University of Connecticut School of Medicine and Dentistry

Louise D. McCullough
University of Connecticut School of Medicine and Dentistry

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Stroke in Women: Disparities and Outcomes

Rebecca W. Persky, **Lisa Christine Turtzo**, and **Louise D. McCullough**
Departments of Neurology and Neuroscience, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030, USA

Abstract

Stroke is the leading cause of disability in the United States and affects 15 million people worldwide. Studies performed in various parts of the world have found differences between sexes in stroke incidence, prevalence, mortality, and outcomes. Although men are at higher risk of stroke for most age groups below age 85 years, after this age the incidence reverses dramatically, with women being much more at risk. Furthermore, recent studies suggest that women have worse recovery than men post-stroke. Many aspects of recovery may influence this outcome, including sex-specific comorbidities, aggressiveness of acute treat-ment, prevention therapies, and varying degrees of social support and rates of depression. It is important to further define and investigate sex differences in stroke incidence, care, treatment, and outcomes to improve functional recovery in women.

Introduction

Stroke is the third leading cause of death after heart disease and cancer, and the leading cause of disability in the United States. During most of the life span, men have a higher incidence of stroke than women, but over the age of 85 years more women suffer strokes (Fig. 1)[1•], leading to an excess of disability and mortality in older women. Several studies suggest that women may be treated less aggressively for primary and secondary stroke prevention and acute stroke compared with men. Women also have higher rates of depression and lower quality of life than men and are more likely to require assistance after a stroke, even when controlling for factors such as age and premorbid function. As our population ages, elderly women will become an increasing proportion of the stroke population, making it crucial to identify and address these disparities. Additionally, sex differences may exist in the efficacy of pharmaceutical agents used for stroke prevention and treatment or in the effectiveness of rehabilitation. Identifying these differences will allow us to tailor therapy to the specific needs of women and enhance functional outcomes. This article discusses recent evidence demonstrating the existence of sex disparities in stroke care and recovery. Possible differences in "sex-based biology" could account for some of these disparities. We hope that a better understanding of these differences will allow for more appropriate treatment and prevention for women and men.

Incidence and Prevalence

Historically, male sex has been considered a risk factor for stroke; however, because of the longer life expectancy in female individuals, the majority of stroke deaths now occur in women [2]. Every year 55,000 more women suffer a stroke than men. Although stroke incidence rates are higher for men than women in most age groups, after the age of 85 years significantly more women suffer strokes than men (Table 1,Fig. 1) [1•]. These sex differences will be magnified

lmccullough@uchc.edu .

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as our population ages, so that by the year 2050, 60% of stroke patients will be women [2]. Addition-ally, more women than men suffer recurrent strokes within 5 years after their first stroke, a finding seen in younger (40–69 years old, 22% vs 33%) and elderly (>70 years old, 28% vs 33%) patients [3••]. Prevalence rates for stroke follow a similar pattern. In an age-adjusted study of pooled data from 13 prevalence studies, stroke is 41% more prevalent in men than women, but reverses dramatically over the age of 85 years [4]. However, this epidemiology may be changing because stroke incidence is rising in younger women. A recent study found that more women 45 to 54 years of age suffer strokes than men in the same age group, which may be indicative of growing rates of obesity and metabolic syndrome in middle-aged women [5].

Severity, Mortality, and Case Fatality

Data vary as to whether there is a difference in stroke severity between men and women. Some studies indicated that women suffer more severe strokes than men [4,6], whereas others found no significant difference between the sexes [7,8]. However, most researchers agree that disability, mortality, and case fatality are greater in women than men, which are confounded by the overall older age of women at stroke onset [2]. As of 2005, stroke accounted for 1 of every 17 deaths in the United States, with women accounting for 60% of stroke deaths (Table 1)[1•]. This disproportionate mortality rate in women is mostly because of the older age of women at stroke occurrence and the fact that women live longer than men. Age-adjusted studies indicate a slightly lower mortality rate for women overall [2], although over the age of 85 years, women still have a 15% higher stroke mortality than age-matched men [9].Multiple studies indicate that the excess of women who die from stroke is increasing dramatically [2,9].

Various studies also have looked at case fatality rates by sex and found no significant difference between men and women or that women had slightly higher rates [2]. A compilation of multiple case fatality studies showed that women have a higher rate of fatality in 26 out of 31 studies that followed patient outcome for 28 or 30 days post-stroke [4]. The International Stroke Trial found higher case fatality rates for women at 14 days and at 6 months post-stroke, but when differences such as age and comorbidities were normalized between the sexes, the higher fatality in women was negated at 6 months post-stroke [3••]. The Women's Health Organization MONICA Project performed a 28-day monitoring of stroke patients and found women to be equivalent or higher than men in case fatality rates [2]. A recent Framingham Heart Study found no significant difference in case fatality rates for 30-, 90-, and 180-day studies [7]. Baseline differences between men and women (eg, age, comorbidities, severity, and pre-stroke disability) cause much of the excess of mortality in women. However, even when controlling for these factors, women continue to have poorer functional outcomes after stroke [10].

Symptoms, Stroke Subtype, and Presentation

Studies have shown that women differ from men in pre-existing comorbidities, stroke subtype, and symptoms on presentation. Women are more likely to have a past medical history of hypertension and atrial fibrillation (AF), whereas men are more likely to present with heart disease, dyslipidemia, diabetes, myocardial infarction, peripheral artery disease, tobacco and alcohol use [2,8,11]. AF itself is a risk factor for stroke with an age-adjusted risk ratio of 4.8 [3••], but a sex disparity is observed in stroke risk for men and women with AF. Although men have a higher incidence of AF at all age groups [12], women with nonvalvular AF have double the risk of stroke than men with the same condition [2]. Women with coronary artery disease and AF have five times the risk of stroke as a healthy individual, whereas risk only doubles in men with both these risk factors [11]. In a study of 780 AF patients on anticoagulation therapy, 40 patients suffered ischemic events, with a relative risk ratio in female versus male patients

of 2.0 (95% CI, 1.3–3.1) [13]. Additionally, women suffered more severe and disabling strokes than men despite the same anticoagulation level [13]. A study that monitored patients who had recently been taken off anticoagulants showed that women had a higher annual incidence of thromboembolic complications than did men [3••]. It is unfortunate that although women are at higher risk for a stroke if they have AF, many women do not perceive themselves to be at risk. A recent study surveyed 215 predominately white, high-earning, well-educated women whether they considered their personal medical conditions as risk factors for stroke [14]. Only 5.4% identified AF as a risk for stroke, and only 15.5% identified their heart disease as a risk factor for stroke [14]. Judging from this data, it is vital to educate high-risk patients about the possible medical consequences of their disease, espe-cially because we now have treatment options for patients with acute stroke.

Similar to reports in the cardiology literature [15], women are more likely to present at hospitals with “nontraditional” stroke symptoms [16]. Of 461 patients in Michigan, 51.8% of women reported nontraditional symptoms, most commonly mental status change, compared with 43.9% of men. The odds of reporting at least one nontraditional symptom was 1.42 times greater in women than in men [16]. Other nontraditional symptoms include pain, lightheadedness, headache, and other unclassifiable neurologic and non-neurologic symptoms [3••,16]. However, other studies found no differences between sexes in traditional stroke symptom presentation [17]. Another study found that although women may more often present with nontraditional symptoms, this sex difference did not lead to any differences or delays in treatment [18••].

Although data vary on the subject of sex differences in stroke subtype, it has been noted that women suffer more cardioembolic strokes than men, [3••,4,17], and have higher rates of subarachnoid hemorrhage [4]. As far as other stroke subtypes, data are variable; some show no difference between men and women [7], whereas others suggest that men are more likely to have large vessel and small vessel strokes, as well as intracerebral hemorrhage [4]. It is important to clarify any differences in etiology because they could lead to changes in acute management or preventive measures.

Prevention

Differences in Response to Pharmacologic Agents

Pharmacologic agents that are commonly used to prevent stroke can display sex-specific effects [3••]. This may reflect differences in drug metabolism or dosing, sex-specific steroid interactions, or other sex-specific differences. It is important to consider the organizational effects of steroids (in prenatal and neonatal life) and activational effects (throughout the life span, beginning at the pubertal surge until menopause) as well as the effects of the sex chromosomes themselves on stroke. In development, the chromosomal sex (XX or XY) programs cells to respond in a certain way to ischemic stress. Neonatal female subjects appear to have an “intrinsic” neuroprotective phenotype, likely due in part to early hormonal exposure but possibly also due to contributions from genes on the X chromosome [19]. Interestingly, women with Turner syndrome (having only one X chromosome) have higher rates of stroke, hypertension, and heart disease, even after they are supplemented with estrogen [20]. This suggests that the presence of a second X chromosome reduces stroke risk, or that the Y chromosome enhances ischemic sensitivity. Emerging data have shown that numerous genes on the second X chromosome escape “inactivation” and may contribute a large degree of heterogeneity in stroke risk and ischemic damage [21]. The “chromosomal” basis of stroke sensitivity and hormonal influences on genetic risks will be a major area of research in the future.

Primary Prevention

Investigators only recently began to examine sex differences in the efficacy of pharmacologic agents used for treating or preventing stroke. The Women's Health Study examined aspirin as a primary preventive agent for cardiovascular disease in healthy women over age 45 years [3••]. The risk of ischemic stroke was reduced by 24% in the treated cohort, but no benefit was found for cardiac risk. A similar male-only cohort (Physicians' Health Study) found a significant risk reduction in a man's risk for cardiac disease, but surprisingly no risk reduction in stroke [3••]. These findings were confirmed in a recent meta-analysis of six randomized trials; women had a 17% reduced risk of ischemic stroke when taking aspirin for primary prevention with no change in ischemic stroke risk in men [2]. In contrast, the risk of myocardial infarction was reduced by 32% in men, with no change in women's myocardial infarction risk with aspirin treatment. Why phenotypic variance in vascular disease manifestations is seen is not yet known [2]. Examination of other antiplatelets and pharmacologic agents for possible differential effects is important to treat patients optimally and efficiently.

Secondary Prevention

Different risk factor profiles in men and women may necessitate different approaches to secondary prevention of stroke. Women are more likely to have hypertension and AF compared with men [2,8,11]. Despite these risk factors, according to one recent study, women are less likely to receive angiotensin-converting enzyme inhibitors after stroke [22]. A discrepancy in the current literature exists regarding whether antiplatelets and anticoagulants are administered differently to men and women after stroke [2,8,22]. Although some studies found no differences [1•,13], studies from other geographic regions found different prescribing practices for men and women [2,8,17]. These differences may reflect different geographic practice patterns. Regardless of biologic sex, patients with risk factors such as hypertension and AF should be treated appropriately to reduce their risk of stroke.

Lipids are generally more aggressively treated in men in the hospital after stroke, perhaps because of the higher incidence of dyslipidemia in men than women at stroke presentation. This is mirrored by the higher percentage of men discharged on statins than women [22]; however, other researchers found men and women are equally likely to be treated with statins, suggesting this may be secondary to geographic variability in prescribing patterns [2]. In addition, women tend to have higher high-density lipoprotein levels than men, and low-density lipoprotein levels often do not begin to rise until after menopause (an average of 2 mg/dL between the ages of 40–60 years) so age becomes an important confounder in these studies [23], and lower rates, especially in younger women, may be appropriate. Importantly, triglycerides may be a more important marker for vascular risk (high triglyceride/low high-density lipoprotein; metabolic syn-drome), although the specific effects on stroke risk have not been evaluated. It is clear that women do benefit from statin therapy as much as men for the prevention of major coronary events [24], and it is likely that the same holds true for stroke.

Sex, Hormones, and Hormone Replacement Therapy

Preclinical data are emerging that suggest that ischemic stress triggers different cell death pathways in male (XY) and female (XX) cells [3••]. If this holds true for clinical populations as well, different "sex-specific" pharmacologic therapies may need to be developed, as an agent may protect one sex and be detrimental in another if the incorrect pathway is targeted. Much of this work has been performed at the bench [25•], and the relevance for patients with stroke, if any, is not yet known. More is known regarding the influence of gonadal hormones on stroke, primarily from large studies performed in the past 5 years [25•]. Pregnancy is also a unique "risk factor" for women, as rates of ischemic (RR, 0.7) and hemorrhagic (RR, 2.5) stroke rise dramatically in the peripartum period [26]. Women with preeclampsia are at higher risk of

stroke for at least 1 year after pregnancy, suggesting that hormonal factors can influence long-term risk [27]. Children born of preeclamptic mothers also experience a higher risk of stroke as adults [28].

Premenopausal women are less likely to suffer a stroke than men of similar ages or postmenopausal women. This difference in epidemiology has been ascribed to the protective effects of estrogen exposure [26,29]. Studies using rodent models have repeatedly shown that females have less damage after an induced stroke than males [3••]. This protection can be reversed with ovariectomy and restored with estrogen treatment [3••].

However, large clinical trials performed over the past 5 years have failed to translate the beneficial effects of estrogen into the population at risk for stroke, postmeno-pausal women. There are numerous potential explanations for these discrepancies, including the timing, dose, and duration of hormone exposure, as well as limitations of our preclinical models (ie, acute treatment after an induced stroke, the use of young animals, primarily rodent studies). For example, the WHI found an increased incidence of stroke in healthy women exposed to hormone replacement therapy (HRT) compared with placebo [30]. However, most women who took HRT in previous observational studies began treatment early in menopause for control of estrogen-deficiency symptoms, whereas WHI subjects began HRT at an average of 12 years after the menopause (mean age for HRT, 63.3 years) [31]. In addition, a recent study by Lisabeth et al. [32] found that women who end their menses between the ages of 42 and 54 years had a lower risk of stroke (hazard ratio, 0.50) than those who went through early menopause before the age of 42 years [32], implying that duration of steroid exposure does influence risk.

Estrogen has adverse inflammatory effects in areas of established atherosclerosis [3••,33, 34•], promoting thrombosis and inflammation in diseased vessels, particularly at supraphysiologic doses. These detrimental effects were seen in the Nurses' Health Study; high doses of estrogen were less protective against vascular disease and promoted stroke risk [35]. The proinflammatory effects are also reflected in C-reactive protein levels, a marker of vascular risk. C-reactive protein was elevated 65% in healthy women (>65 years of age) exposed to 12 weeks of a high dose of estrogen (1 mg/d), and remained 92% higher than placebo even 12 weeks after treatment was discontinued [36].

Because HRT/estrogen replacement therapy's vascular properties may shift from antiatherogenic to proatherogenic in diseased vessels, the KEEPS has been designed to investigate whether initiation of low-dose HRT at an earlier stage of atherosclerosis is beneficial. This trial is a randomized, multicenter trial of HRT in recently menopausal women using oral or transdermal estrogen with intermittent micronized progesterone. Women will be followed for a 5-year period, and common carotid intimal medial thickness as measured by B-mode ultrasound will be used as the primary end point [33]. Additionally, the ELITE is currently enrolling patients. In this trial, postmenopausal women will receive oral 17beta-estradiol or placebo according to their number of years since menopause. It is expected that estrogen will reduce the progression of early atherosclerosis if initiated soon after menopause when the vascular endothelium is relatively healthy.

Acute Treatment

The establishment of Get with the Guidelines-Stroke (GWTG-Stroke) has facilitated the examination of possible sex differences in stroke care in the inpatient setting. Women have longer waiting times once they arrive at the emergency room and receive less intensive treatment and therapeutic workup once they are admitted [10,18••,22]. One recent study found that women had 11% longer door-to-doctor times and 15% longer door-to-image times as men [18••]. These differences have potentially enormous consequences because we have only one

drug to treat patients with acute ischemic stroke, tissue plasminogen activator (tPA). This agent has an extremely short therapeutic window, and even short delays could make patients ineligible. One possible reason for this disparity is the atypical presentations seen in women presenting with stroke, delaying identification of stroke patients [16], although this seems unlikely based on recent data [28]. Women also may experience pre-hospital delay. One study found a three-fold risk of delay in reaching the hospital in women experiencing a stroke compared with men [37], which could increase rates of ineligibility for thrombolytic treatment. Several studies tracking women's awareness of heart disease suggest that, although improved, a significant gap still exists between the perceived and actual risk of cardiovascular disease and stroke, as well as social and behavioral factors that contribute to prehospital delay [14, 38].

Conflicting reports exist in the literature regarding sex differences in rates of thrombolytic administration. In two studies, eligible women were 46% to 60% less likely to receive intravenous (IV) tPA than eligible men; however, these studies reported wide variation in the rates of eligibility and receipt of IV tPA across hospitals within the geographic region [39, 40]. Similar results were found in a recent meta-analysis of published literature [41]. Interestingly, data from 32 academic medical centers found that women and men were equally likely to receive IV tPA in risk-adjusted analyses [42], suggesting that the "gender gap" may be closing, especially at larger academic centers.

According to the most recent American Heart Association statistics based on the GWTG-Stroke program, 71.8% of men and 68% of women arriving within the first 2 h of symptom onset received IV tPA. The difference increased further for patients arriving within 3 h of symptom onset (59.4% vs 55.4%) [1]. This disparity in IV tPA administration is unfortunate considering two recent studies found that IV tPA may benefit women more than men, reversing the poorer outcomes normally seen in women compared with men [43,44•].

Carotid Disease

Sex differences also are present in other treatments for stroke beyond tPA. Female sex is classified as a surgical risk in carotid endarterectomy [3••]. The first clinical trial of carotid endarterectomy, the ACAS, found that women had a death rate and perioperative stroke rate of 3.6% compared with 1.7% in men, which was confirmed by later studies [45]. Therefore, women are less likely to have this procedure performed (0.3% vs 1.5%), which may be appropriate. The benefit of carotid endarterectomy in women experiencing a transient ischemic attack or nondisabling stroke also appears to dissipate within 2 weeks, after which the benefit rapidly declines [3••]. Some researchers suggest that this is because women have a smaller carotid artery than men (40%) [45], which may explain the lack of sex differences in the recent CREST, in which women had no increased risk of death or stroke compared with men (4.5% vs 4.2%) [45].

Quality of Care

The availability of the large GWTG-Stroke registry has allowed for the detection of small differences in the treatment of male and female stroke patients throughout the United States. Unfortunately, women seem less likely to receive defect-free care (66.3% vs 71.1%; OR, 0.86; 95% CI, 0.85–0.87), and are less likely to be discharged home (41.0% vs 49.5%; OR, 0.84; 95% CI, 0.83–0.85) [10]. These differences will need to be closely monitored over the next decade as our population continues to age and even more women are at risk.

Outcomes and Disability

One of the most striking disparities between men and women is the differences in disability and recovery post-stroke. According to a recent Framingham Heart Study, women were more disabled in various functional activities (eg, eating, dressing, grooming, transfer from bed to chair, and walking) during the acute phase of stroke and at 3 to 6 months post-stroke (Table 1) [7]. Multiple studies recently assessed functional outcome based on the Barthel index and found that fewer women overall were independent in activities of daily living than men [2]. Women also are more likely to be discharged into assisted-living facilities or hospices [2,7]. However, when controlling for pre-stroke functional ability, two studies found no sex difference in achievement of independence in activities of daily living, and attributed differences to older age and lower pre-stroke physical function [2,46].

Depression is an area of concern for stroke victims also. Women are more likely to report depression after stroke, which can impair recovery and quality of life. Depression at baseline has been found to be similar between the sexes; however, data from the TAIST showed that even when adjusting for age, stroke severity, and comorbidities, women scored lower than men, particularly in areas such as mental health status [47]. Because of the older age at the time of stroke, women are often living alone and therefore have less social support, which contributes to their being institutionalized at discharge [2,3••]. Based on this observation, researchers have begun investigating social factors related to stroke risk and recovery.

Conclusions

As the population ages, the incidence rate and mortality rate of stroke in women will continue to increase. It is imperative to address many of the aspects in stroke presentation, treatment, and care that may differ in men and women. Attention to these differences will ensure equivalent levels of prevention, acute treatment, and diagnostic testing in men and women. Women are more likely to be disabled after stroke than men. The current literature indicates that this disparity may result from the older age and poorer pre-stroke functional status of women than men at the time of stroke onset; however, even in age-matched cohorts, overall functional status is worse in women than men. Differences in hormone exposure, social networks, and comorbid function may contribute to these sex differences in functional recovery. Differences in sex-based biology also are increasingly recognized. Different strategies (eg, social interaction, treatment of depression) may be more efficacious in women, and rehabilitation strategies may need to be tailored to the specific needs of women post-stroke.

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Clinical Trial Acronyms

ACAS	Asymptomatic Carotid Atherosclerosis Study
CREST	Carotid Revascularization Endarterectomy Versus Stenting Trial
ELITE	Early Versus Late Intervention Trial With Estradiol
KEEPS	Kronos Early Estrogen Prevention Study
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
TAIST	Tinzaparin in Acute Ischemic Stroke Trial

WHI Women's Health Initiative

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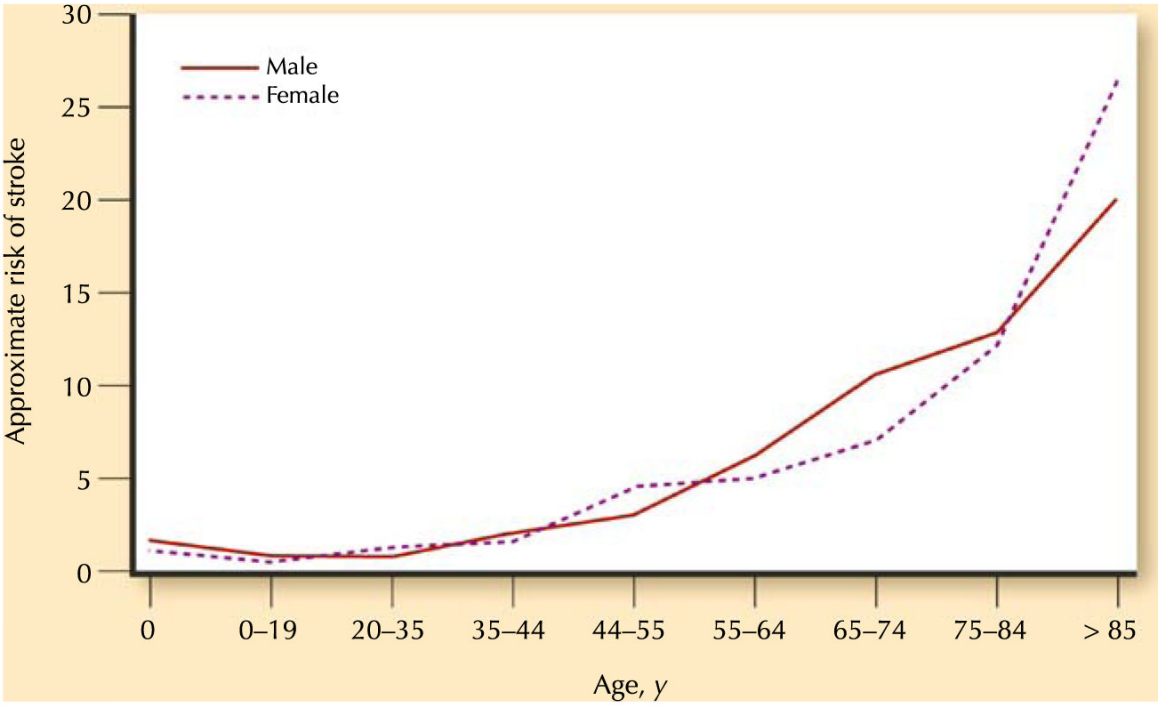

Fig. 1.
Approximate risk of stroke by age and sex. Data were compiled from available sources to estimate the approximate risk of stroke over the life span [1•,6,48–50]

Table 1

Differences in prevalence of stroke, incidence of stroke, disability, and mortality post-stroke between men and women in the United States

	Women	Men
Prevalence (as of 2005), million	3.9	2.6
Average age of first stroke, y	72.9	68.6
Incidence		
55–64 y	–	25% higher
65–74 y	–	50% higher
75–84 y	25% higher	
Disability: 3–6 mo post-stroke, unable to do independently, %		
Eating	15	9
Dressing	37	20
Grooming	32	17
Transfer from bed to chair	32	13
Walking	32	18
Mortality (as of 2005)	86,993	56,586

(*Data from* the American Heart Association [1•], Appelros et al. [4], and Petrea et al. [7].)