Transient Ischemic Attacks

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Transient Ischemic Attacks
Dedication

To my family, Seema, Nikhil, Kavya, and parents Rama and Veena
To my mentors, Marc Fisher, Vladimir Hachinski, and Henry Barnett
S.C.

To my family, Joanne, Aaron, David, and Aliza, and parents Elaine and Hal
To my mentors, Sid Gilman and K.M.A. Welch
S.R.L.

To our patients who have taught us about TIAs
To our readers, who will hopefully practice what is preached here or
at least be stimulated to think critically about TIAs
And to all of our colleagues, whose sense of inquiry, knowledge,
wisdom, and understanding are also contained in this book
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Foreword

Transient ischemic attacks (TIA) may be transient, but the threat that they signal is not. Increasingly we realize that about one-fifth of patients with TIA will suffer a stroke within 3 months, about half occurring in the first week! Thus it becomes imperative that both the public and physicians become familiar with the symptoms and what needs to be done about them. Physicians have a one stop means of doing so, through this volume.

First they will learn about the epidemiology and pathophysiology of TIAs and will become familiar with the diverse cerebral and ocular syndromes. Then they will appreciate the advantages and limitations of different diagnostic modalities. Brain imaging occupies a deservedly prominent place, beside the less used but uniquely and selective, helpful single photon emission computer tomography (SPECT) and positron emission tomography (PET). Cerebrovascular ultrasonography, cardiac diagnostic and coagulation studies are evaluated with equanimous objectivity.

Subsequently the reader becomes acquainted with the indications and controversies surrounding the use of antiplatelet agents. The role of anticoagulants is well justified, while heparin and related compounds are put into proper perspective, given the continuing triumph of hope over evidence. Diabetes treatment while essential, does not have the obvious beneficial effects of antihypertensive therapy. Other medical therapies are also discussed, as well as thrombolysis for TIA and mild stroke.

Next the indications for surgery in stroke prevention and the role of angioplasty and stenting are weighed. Cost effectiveness issues merit a whole chapter and the book ends with a flourish of clinical vignettes.

Throughout, editors and authors strive to base their conclusions on evidence where it exists, and on pragmatism and common sense where it does not. At a time of rising awareness of the peril and opportunities for prevention posed by TIAs, this is a most timely book.

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Preface

This book was born from the synthesis of the rapidly proliferating field of cerebrovascular disease research, excitement about effective new imaging and therapeutic strategies, and the need to timely educate clinicians about the changing playing field for a common, serious, and expensive syndrome—transient ischemic attacks (TIA). TIsAs can now stand on their own as an important and, at times, unique aspect of symptomatic cerebrovascular disease, distinct enough to warrant a textbook in its own right. With new information on a worrisome and serious natural history, growing knowledge of risk factors and their management, sophisticated neuroimaging techniques, and a broadening armamentarium of therapeutic approaches, the clinician is now faced with multiple levels of decision making. Does one admit the patient with a recent TIA to the hospital? What are the optimal imaging and diagnostic strategies? Which antiplatelet agent to use? What is the role for surgery and interventional techniques? How do I optimally control associated risk factors? This book serves to provide the most current information to help guide clinicians through the best decisions to care for their patients, using evidence-based recommendations when available and expert opinion when no good data exist.

Having initiated (SRL with Dr. Lawrence Brass of Yale University), directed, and taught (SRL and SC) the course on TIsAs at the annual American Academy of Neurology meeting for the past several years, it has become clear that clinicians are keen on the latest synthesized data and approaches to the problem of transient cerebral ischemia. They require cutting edge analyses, and express concerns over the lack of consensus in several important areas. Diagnosis and management of TIsAs continues to perplex even the most seasoned clinicians. Further impetus for providing this book includes response to the issues raised over the years at the TIA course, our own clinical and research experience (and those of our colleagues who have generously contributed their expertise to this team effort), the need to handle the TIA patient differently in some regards from the patients with a severe neurological deficit having a similar underlying pathophysiologic mechanism, and the need to bring TIA to its own place in the field of cerebrovascular disease.

This book is intended to be a one-volume, highly readable source of current, accurate information for the clinician and clinical stroke researcher,
that can readily answer questions that arise, provide guidance in patient care, and establish quickly what we do and do not know in the field. We have chosen esteemed colleagues from the field to address all of the important topics that serve as chapters. They have each helped create a perspective that will provide the clinician important and useful information in a readily available format. Our wish is that patients will directly benefit from the knowledge imparted such that they will never suffer from the consequences of a disabling stroke.

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Clinical Background
Introduction

A transient ischemic attack (TIA) can be defined as a sudden focal loss of neurological function with complete recovery within 24 h, caused by inadequate perfusion in the partial or complete distribution of the carotid or vertebrobasilar arteries [1]. TIAs may involve either the brain or the retina. Transient monocular blindness (TMB) caused by retinal ischemia has also historically been known as amaurosis fugax and the terms are often used synonymously [2]. Nonspecific neurological complaints such as dizziness, isolated vertigo, presyncope, syncope, or confusion should not be considered TIAs without other substantiating evidence.

The maximal duration of symptoms caused by a TIA has been arbitrarily set at 24 h, although most last less than 30 min [3]. Deficits caused by cerebral ischemia lasting more than 24 h but less than 3 weeks are sometimes called a reversible ischemic neurological deficit (RIND), but contemporary cross-sectional brain imaging studies have shown these to represent minor strokes and this terminology is now infrequently used. Computed tomography (CT) studies and particularly diffusion weighted (DWI) magnetic resonance imaging (MRI) have also shown that many symptoms clinically suggestive of TIA are actually minor ischemic strokes (or cerebral infarctions). Although some data suggest that TIAs of longer duration are more likely to correspond to infarction on imaging, other investigators have been unable to distinguish clinically TIAs with and without infarction [4–7].

The question thus arises whether TIAs should continue to be defined clinically or only in conjunction with neuroimaging studies which fail to show infarction. CT scanning, though easily obtainable, lacks sensitivity and specificity for both the presence and timing of infarction. Diffusion weighted MRI would be more useful. Imaging all TIA patients with MRI
would be cumbersome, expensive, and logistically impossible in many clinical situations. Therefore, the compelling reason to redefine TIAs based upon MRI findings would be prognostic differences between TIAs (more strictly defined) and minor ischemic strokes.

An analogous question concerns the practical usefulness of distinguishing clinically between minor ischemic stroke and TIA. Several community and hospital-based studies suggest that the stroke risk of patients with clinically diagnosed TIA is comparable to those with RIND or minor stroke, especially if patients with amaurosis fugax are excluded [8–10]. Treatment trials often include TIA and minor ischemic stroke patients under this assumption, and terms such as ‘reversible ischemic attacks’ have been proposed to cover both categories, although the traditional categories of TIA and minor stroke have also been defended as useful in both differential diagnosis and case–control studies [2]. A very small number of minor strokes and symptoms suggesting TIA are caused by intracerebral hemorrhage. These small hemorrhages are readily identified by CT imaging, which is important given that they differ in etiology, prevention, and optimal management.

**TIA incidence, prevalence, and risk factors**

The incidence of TIA is defined as the proportion of a population experiencing a first TIA in a given period of time (usually a year). The point prevalence of TIA is the number of people in a defined population, at a given point in time, who have ever experienced a TIA. In each instance individuals who have suffered a stroke are usually excluded. Both definitions may also be modified in rather complex ways which can vary between studies and (presumably) influence outcome. For example, incidence studies may ‘count’ TIAs which occur prior to a study period and bring the patient to a physician, while ignoring prior TIAs which did not prompt medical evaluation [11]. Many studies do not explicitly define the inclusion criteria used.

Several factors make TIA incidence and prevalence studies challenging. The symptoms of TIAs, being transient by definition, may not prompt an affected individual to seek medical attention. The diagnosis of a TIA is strictly clinical, and historical details may become blurred with time. There are also many nonspecific symptoms common in the elderly (such as dizziness, vertigo, syncope, confusion, and gait disturbance) which may be mistaken for a TIA. Hospital dismissal summaries and medical records used to identify stroke (and by reasonable inference TIA) are liable to error [12]. Finally, interobserver reliability in the diagnosis of TIA, even amongst neurologists, has proven less than ideal [13,14].

With these limitations, a number of studies of varying design have reported the incidence and prevalence of TIAs. In theory the best approach
would utilize a population-based, observational study of individuals with easy access to medical care and a demographic mix allowing conclusions to be drawn about groups of different age, race, gender, and socioeconomic status. No single study satisfies all of these criteria.

**Incidence**

In Rochester, Minnesota, the Rochester Epidemiology Project Medical Records Linkage System allows retrospective identification of nearly all cases of stroke and TIA that occur in a defined population. The most recent study of TIA epidemiology in Rochester produced a crude TIA incidence rate of 68 per 100,000 persons per year for the years 1985–1989 after age and sex adjustment to the 1980 US white population [15]. As expected, age-specific rates showed increasing incidence with increasing age to a maximum of 584 events per 100,000 persons 75–84 years old, after which age the rate declined slightly. This ‘incidence decline’ in the ‘oldest old’ has been noted in other studies and may be explained by several issues. While the incidence may truly decline in those people who have survived to age 85 and beyond, other explanations include lack of complete case ascertainment in the oldest members of the population, in this relatively small population [11,16,17]. While the age-adjusted incidence rate for TIA in Rochester was slightly higher for men than for women (76 vs. 62 per 100,000), the difference was not statistically significant. This is in accordance with other studies which show roughly equivalent rates between sexes, although women tend to be older at the time of the incident event [11,16,17].

TIA incidence data from Rochester for 1985–1989 are summarized in Table 1.1. Comparison of data from the Rochester linkage system for the years 1955–1969 with the more recent data reveals some discrepancy, with crude age and sex-adjusted incidence rates rising from 33 per 100,000 to 68 per 100,000 [18,19]. The lower incidence rates in the earlier study have been attributed to methodological issues in case ascertainment. This is supported by a cohort study from 1960 to 1972 (without such methodological issues) that produced incidence rates comparable to the recent data [20].

Crude age and sex-adjusted incidence rates from other population-based studies cluster around those of the earlier Rochester report [11,21–25] (Table 1.2). While actual differences in TIA incidence are possible, this would seem an unlikely explanation, especially as stroke incidence in Rochester is not significantly higher than at other sites (discussed under epidemiology of cerebral infarction). Differences in population type, methods of case ascertainment, and incomplete case ascertainment would be more plausible.

A breakdown of TIA incidence by arterial distribution in the Rochester population is shown in Table 1.3 [15]. The high percentage of carotid
A small Japanese study with only 18 total events found a more even balance between anterior and posterior circulations [11,22,24,25].

Rates of amaurosis fugax have not been commonly reported in TIA studies. The age and sex-adjusted incidence of amaurosis fugax in Rochester from 1985 to 1989 was 13/100 000, accounting for 18% of TIAs [15]. A prospective Danish study found an incidence of 7/100 000, but estimated the ‘true’ incidence to be 14/100 000 based upon poor case ascertainment in the elderly [26]. In Oxfordshire, England, and Umbria, Italy, amaurosis fugax accounted for 17% and 5.3% of all TIAs, respectively [11,17]. In Segovia, Spain, only one of 103 TIAs recorded was isolated amaurosis fugax [16].

While nonspecific transient neurological symptoms such as dizziness and visual disturbance seem ubiquitous in the elderly population, one study found the prevalence of ‘transient neurological attacks’ (TNAs) to be similar to that of typical TIA in older persons (1.6%) [27]. ‘Atypical TIAs’ have been found to carry a lower risk of future stroke and a higher risk of future cardiac events compared with ‘typical’ TIAs [28].

Although there is limited longitudinal data regarding TIA incidence, and comparisons between studies suffer from differences in case ascertainment and statistical methods, data from Rochester and other sites suggests that the TIA incidence rates have been stable over time [15,25,29]. This contrasts with an apparent decline in the incidence of stroke from the 1950s through the mid early 1980s, with the subsequent end of the decline in the 1980s and early 1990s (see epidemiology of cerebral infarction).

### Table 1.1 Average annual age- and sex-specific incidence rates* of transient ischemic attack in Rochester, Minnesota, 1985–1989

<table>
<thead>
<tr>
<th>Age group</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
</tr>
<tr>
<td>45–54</td>
<td>54</td>
<td>8</td>
<td>57</td>
</tr>
<tr>
<td>55–64</td>
<td>128</td>
<td>14</td>
<td>96</td>
</tr>
<tr>
<td>65–74</td>
<td>323</td>
<td>24</td>
<td>277</td>
</tr>
<tr>
<td>75–84</td>
<td>687</td>
<td>26</td>
<td>539</td>
</tr>
<tr>
<td>≥ 85</td>
<td>498</td>
<td>6</td>
<td>467</td>
</tr>
<tr>
<td>All†</td>
<td>76</td>
<td>6</td>
<td>62</td>
</tr>
</tbody>
</table>

*Per 100 000 population.
†Rates are age-adjusted or age- and sex-adjusted to 1980 US white population.

Table 1.2 Comparison of incidence of transient ischemic attack (TIA) reported from sites throughout the World

<table>
<thead>
<tr>
<th>Location</th>
<th>Time period</th>
<th>Study type</th>
<th>Case no.</th>
<th>Incidence rate (crude, unadjusted by age, per 100 000)</th>
<th>Age/sex-adjusted incidence rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>1955–1969</td>
<td></td>
<td>198</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>1996–1997</td>
<td></td>
<td>89</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>1983–1986</td>
<td></td>
<td>53</td>
<td>56</td>
<td>45</td>
</tr>
</tbody>
</table>

*Age- and sex-adjusted to 1980 US white population, per 100 000 population. NR, Not reported.

Prevalence

Studies of TIA prevalence are more difficult and probably more inaccurate than those of TIA incidence [30]. Estimates of prevalence have varied widely but tend to run between 1% and 6% of different populations. As expected, prevalence has been shown to increase with age. Graphic representation of some estimated prevalence rates by age group can be seen in Fig. 1.1 [27,31–37].

Risk factors

A risk factor for a disease is defined as a characteristic of an individual or a population which indicates that the individual (or population) has an increased risk of disease compared with individuals (or populations) without that characteristic [30]. This implies, but does not establish, that the risk factor plays a causal role in the development of the disease (as the risk factor and disease may both be linked to a separate underlying cause). Knowledge of risk factors can help physicians predict a person’s chance of developing disease and lead to risk factor modification.

Risk factors for TIA have been less well defined than those for stroke or ischemic cardiac disease for several reasons. A TIA is less disabling (by definition) than stroke or cardiac events; TIAs are less common than these entities, thereby hindering cohort studies; and TIAs are often elusive and difficult to classify for reasons discussed previously. Finally, it can be argued that risk factors for TIA are only important insofar as TIA itself is a risk factor for ischemic stroke, an important cause of disability and death.
Fig. 1.1 Prevalence of transient ischemic attacks (TIA) in selected population-based studies among (a) men and (b) women. Reprinted with permission, from Bots ML et al. Transient neurological attacks in the general population. Stroke 1997; 28: 768–73.
However, while it may be true that TIAs alone are of little concern, by studying TIA risk factors one may be able to identify causal mechanisms which are preferentially found in the TIA population but diluted in a larger study of stroke. It is currently unknown whether the mechanisms causing TIA (cardioembolism, large vessel atherosclerosis, small vessel disease, etc.) mirror the mechanisms causing ischemic stroke in type or distribution. If these mechanisms and their associated risk factors differ, treatment and prevention strategies might differ for TIA patients, ischemic stroke patients without TIA, and the general population at risk of stroke.

Studies have not consistently identified differing risk factors between cerebral infarction and TIA. Atrial fibrillation was more common in stroke than TIA patients in some hospital-based studies, but this difference has not been documented in population-based studies and so it is possible that this reflects referral bias [9,38]. A population-based case–control study in Rochester found that the odds ratios for TIA risk factors such as ischemic heart disease, hypertension, atrial fibrillation, diabetes, and cigarette smoking were similar to those produced in an earlier study of ischemic stroke; lipid status, homocysteine levels, and alcohol intake could not be assessed [39,40]. In the Oxfordshire Community Stroke Project (OCSP) the only significant difference in risk factors for TIA and minor ischemic stroke was higher cholesterol levels in the TIA group [9]. Higher cholesterol levels were also found among TIA patients in a hospital-based referral study [41]. The role of cholesterol in stroke and TIA is complex, but one can speculate that higher cholesterol levels predispose patients to carotid atherosclerosis, and that carotid stenosis is a proportionately more common cause of TIA than ischemic stroke. Large vessel atherothrombotic stroke is more commonly preceded by TIA than cardioembolic or lacunar stroke, supporting this contention (see Table 1.4).

<table>
<thead>
<tr>
<th>Series</th>
<th>Atherothrombotic cerebral infarct (%)</th>
<th>Embolic cerebral infarct (%)</th>
<th>Lacunar cerebral infarct (%)</th>
<th>Intracerebral hemorrhage (%)</th>
<th>Subarachnoid hemorrhage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard Stroke Registry</td>
<td>50</td>
<td>23</td>
<td>11</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Stroke Data Bank</td>
<td>20</td>
<td>13</td>
<td>13</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Lausanne Stroke Registry</td>
<td>29</td>
<td>30</td>
<td>14</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Feinberg WM et al. Guidelines for management of transient ischemic attacks: from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks. Circulation 1994; 89: 2950–65, with permission.
Given the limited data about risk factors for TIA per se, it is reasonable to examine risk factors for ischemic stroke, where much more information is available. Well-established nonmodifiable risk factors for ischemic stroke include increasing age, male sex, positive family history, and race (blacks and Hispanics vs. whites in the USA) [42–44]. The increased incidence of stroke among blacks is due, in part, to a higher stroke burden in younger persons [45]. While some of this difference can be attributed to other risk factors such as hypertension and diabetes, a substantial proportion remains unexplained [46]. The incidence of stroke (particularly intracerebral hemorrhage) is higher in Asians than whites, but this may be more related to environmental and lifestyle factors than race.

Well-established modifiable risk factors for ischemic stroke include diastolic and systolic hypertension, cardiovascular disease, diabetes, cigarette smoking, significant carotid atherosclerosis, and (likely) hyperhomocysteinemia. TIA as a risk factor for stroke will be discussed in the section on prognosis. Within the realm of cardiovascular disease, atrial fibrillation, mitral stenosis, congestive heart failure, left ventricular hypertrophy and recent large myocardial infarction are established risks [47,48]. Much recent attention has been paid to less well-defined cardiovascular risks such as patent foramen ovale (PFO), atrial septal aneurysm, spontaneous echocardiographic contrast, valvular strands, mitral valve prolapse, and aortic atherosclerotic debris, but their role in stroke (and TIA) is controversial. For instance, in the case of PFO, case–control studies have shown a higher incidence of PFO in patients with stroke than in controls, and in patients with cryptogenic stroke than in patients with stroke of known cause [49–51]. However, control patients have not been randomly selected and evaluation may not be as aggressive for intracardiac shunts during their studies. Emerging evidence suggests that PFO may not be more common in stroke patients than the general population [52,53]. Other less well-defined stroke risk factors include oral contraceptive use, excessive ethanol consumption, illicit drug use, physical inactivity, obesity, hyperinsulinism, migraine, and hematological abnormalities such as antiphospholipid antibodies, elevated fibrinogen levels, and genetic defects in coagulation cascades [47].

The status of elevated total serum cholesterol as a risk factor for ischemic stroke is not clear. While elevated serum cholesterol plays a definite role in coronary artery disease (CAD), it has not been consistently linked to ischemic stroke in epidemiological studies [54,55]. Meta-analyses of cholesterol reduction with older agents failed to show any benefit upon stroke; conversely, in studies designed primarily for coronary artery disease, the newer ‘statin’ drugs have reduced rates of ischemic stroke [56–58]. The difference may be due to relative potency in cholesterol reduction [59]. Alternatively, there may be other class-specific causal mechanisms involved, such as stabilization of plaque components or
antiplatelet action [48]. As with other preventative measures for stroke, the benefit of statin agents is modest, with an absolute risk reduction of < 1% per year in secondary prevention trials for CAD [59]. Low total serum cholesterol has actually been linked with increased risk of intracerebral hemorrhage [60]. Prospective studies of statins in secondary stroke prevention are underway.

**Prognosis following TIA**

The prognosis following TIA is an issue of vital importance to patients, their families, and the physicians providing their care. Such information helps determine the rate and scope of diagnostic evaluation for TIA patients, the mode and aggressiveness of their treatment, and the importance of TIA in the realm of public health. The value that patients assign to prognostic information on a personal level, even without treatment implications, should not be underestimated.

Like studies of TIA incidence, studies of prognosis after TIA would ideally be large, prospective, and population based. Such population groups will necessarily include patients receiving a variety of medical and surgical therapies, and thus will not provide true natural history data, which at this time would be impossible and unethical to obtain. Definitions again are important, because patients may be included or excluded from consideration based upon the nature of their symptoms, the methods of their treatment, prior history of TIA, prior history of stroke, or imaging abnormalities [61]. Statistical methods must be sound. In many studies stroke occurrence following TIA is expressed as subsequent strokes divided by the original number of enrolled patients. By ignoring non-stroke deaths (and thus patients no longer at risk of stroke), these studies will underestimate stroke risk. Occurrence of stroke and survival should therefore be determined with actuarial methods [62]. Adequate and reliable follow-up is essential.

A summary of prognosis following TIA is given in Table 1.5.

**Community-based studies**

Data on prognosis after TIA comes from the OCSP, which has reported on a population-based cohort of 184 patients with incident TIAs who were observed prospectively for a mean of 3.7 years [63]. Only one patient was lost to follow-up. At some point during follow-up, treatment included aspirin in 105 patients, warfarin in 15 patients, and carotid endarterectomy in six patients.

In this study the probabilities of stroke, death, and myocardial infarction were elevated compared with the general population. Risk of death at 5 years was 31.3%, with an annual risk of 6.3% and an overall risk ratio of
Table 1.5 Prognosis following transient ischemic attack (TIA) in selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Average annual death risk*</th>
<th>Stroke risk at selected time intervals after TIA</th>
<th>Average annual stroke risk*</th>
<th>Average annual MI risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population-based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxfordshire, UK [63]</td>
<td>184 TIA</td>
<td>6.3%</td>
<td>4.4%</td>
<td>8.8%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Rochester, MN [62]</td>
<td>352 TIA</td>
<td>6.8%</td>
<td>7%</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Hospital-based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnston [70]</td>
<td>1707 TIA</td>
<td>2.6% at 3 months</td>
<td>5.3%</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>Hankey [68]</td>
<td>469 TIA</td>
<td>4.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation:</td>
<td>592 TIA or minor ischemic stroke, NRAF, controls</td>
<td>9–12%</td>
<td></td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>EAFT Study Group [82]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NASCET [77]</td>
<td>331 TIA or nondisabling ischemic stroke, 70–99% ICA stenosis, controls</td>
<td>3.2%</td>
<td></td>
<td>13.8% (any)</td>
<td>13% (ipsilateral)</td>
</tr>
</tbody>
</table>

MI, Myocardial infarction; EAFT, European Atrial Fibrillation Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NRAF, nonrheumatic atrial fibrillation; ICA, internal carotid artery.
*Risks documented are arithmetic average annual risks.
1.4. Cardiac disease and sudden death accounted for 35% of fatalities, while stroke accounted for 31%. Stroke was more common than expected in the population, with a 5-year probability of 29.3% and a mean risk of 5.9% per year. Importantly, the danger of stroke was most notable in the first year, with risks of 4.4%, 8.8%, and 11.6% at 1, 6, and 12 months, respectively. The risk ratios for stroke compared with the general population were 13.4 over the first 12 months and 7.0 over 7 years. The risk of myocardial infarction was somewhat lower at 12.1% over 5 years, while the combined annual risk of death, stroke, or myocardial infarction was 8.4%.

In Rochester, outcome data from a large, retrospective, population-based study of incident TIAs [62] demonstrate findings in close agreement with those from Oxfordshire. The risk of death at 5 years was 34%, producing a risk ratio of 1.5. Cardiac deaths were again more common than stroke deaths (41% vs. 31%). Risk of stroke at 5 years (given survival) was 28%, with a mean yearly risk of 5.6%. The probability of stroke at 1, 6, and 12 months in Rochester was 7%, 10%, and 13%, respectively. This resulted in risk ratios of 101, 25, and 16 compared with the general population, again emphasizing the importance of the first months following TIA. The slightly lower early stroke risk in Oxfordshire may be a methodological artifact, as incident TIAs in their study were not necessarily first-ever TIAs, and there was an average 3-day interval between the index TIA and enrollment.

Other population-based studies have published prognostic data which are limited by smaller numbers or short follow-up period [17,22,34,64].

**Hospital-based studies**

Hospital-based TIA studies necessarily suffer from referral bias and thus are less generalizable than population-based studies. Hospital-referred patients tend to be younger and therefore less likely to suffer from atrial fibrillation and other comorbidities. They are often entered into studies longer after qualifying TIAs, thus selecting out patients who suffer strokes in the interim [65]. In contrast to the population-based studies discussed above, TIAs are not necessarily incident events, and prior stroke may be allowed. However, the information provided by hospital-based studies about selected groups can be quite useful.

Among prospective hospital-based studies with greater than 100 patients, annual risk of death over 5 years has ranged from 3.5% to 4.5% [66–68]. Illustrating the importance of methodology, the study by Heyman *et al.*, which reported a low mortality, did not include TIA patients with symptoms attributable to cardiogenic emboli or ‘nonatherosclerotic etiology’ or those who had EC-IC bypass. Two studies including patients with RIND found annual mortality rates of 2.2% and 5.9%, with no statistically significant difference between TIA and RIND patients in the former [10,69].
Risk of stroke in the two large prospective TIA studies reporting data was 3.4–4.5% annually (with the caveats previously noted) [66,68]. As in the population-based studies, the greatest risk of stroke came shortly after TIA. In the group reported by Heyman, a good deal of the initial risk was iatrogenic secondary to invasive diagnostic and treatment modalities. Annual stroke risks in the studies combining TIA and RIND discussed above have been calculated at 2.2% and 5.6% [61].

A large, retrospective, emergency department (ED)-based cohort study of TIA by Johnston and colleagues has evaluated risk of stroke and other adverse events following TIA, and potential predictors of stroke [70]. Among 1707 patients with TIA diagnosed in an ED of one of 16 California hospitals in a single health maintenance organization (HMO), crude (non-actuarial) stroke risk over 90 days was 10.5%, with half of strokes occurring in the first 2 days. Two hundred and sixteen patients (12.7%) experienced recurrent TIA, 44 (2.6%) were hospitalized for cardiovascular events (congestive heart failure most commonly) and 45 patients (2.6%) died. More deaths were due to stroke (n = 20) than cardiovascular events (n = 9). Adverse events, including stroke, recurrent TIA, cardiovascular hospitalization, or death, occurred in 25.1% of patients, with more than half of adverse events occurring in the first 4 days. Review of cases with questionable diagnoses identified 96 patients felt not to have had TIA but rather syncope, migraine, neuropathy, etc. Three had a stroke in the subsequent 90 days. Their exclusion from the larger group did not produce a different overall stroke risk. Among 182 patients lacking documentation of symptom resolution within 24 h of presentation, 19 (10.4%) suffered a stroke during follow-up. The number of iatrogenic strokes was not disclosed, although follow-up was terminated if endarterectomy was performed. Factors noted at the occurrence of TIA which predicted an increased risk of subsequent stroke included: age > 60 years [odds ratio (OR) 1.8], diabetes mellitus (OR 2.0), symptom duration > 10 min (OR 2.3), and weakness (OR 1.9), or speech impairment (OR 1.5) as a symptom of the TIA.

These stroke risk data do not markedly differ from those noted in large population-based studies. In Rochester the 1- and 6-month stroke risks after TIA were 7% and 10%, given survival. The figures were somewhat lower in Oxfordshire for reasons described. While the use of HMO ED patients presents some selection bias, it is probably less than for hospital referrals. The fact that prior stroke was not an exclusion criterion might reduce direct comparison with population-based studies, but is useful in its own right. Most importantly, this study has shown that the early risk of stroke following TIA is considerable. The conclusion that TIA patients often have cardiac conditions is also well known, but easily overlooked by neurologists and internists focusing upon the patient’s presenting neurological symptoms. TIA is not a benign condition even in comparison with significant cardiovascular disease. In a case–control study comparing
280 TIA patients with 399 cardiac patients undergoing catheterization, the TIA patients were more likely to suffer from stroke or myocardial infarction within 3 years. The hazard ratio for death for TIA patients was 1.3 after adjustment for age, race, sex, and ‘major cardiovascular risk factors’. Only the difference in all-cause mortality failed to reach statistical significance [71].

Whether this enhanced knowledge about timing of stroke risk and cardiovascular comorbidity in TIA patients can be translated into improved outcome through expedited medical or surgical management or screening is unknown. Future prospective clinical trials would be helpful in this regard.

**Treatment trials**

The exclusion criteria in TIA treatment trials are usually more strict than hospital referral studies, and necessarily more strict than population-based studies. In addition to restrictions set upon age and medical comorbidities, time lag is again important, with many patients passing through the window of highest risk before enrollment and randomization. The goal of treatment trials is comparison of treatment groups rather than general prognosis. Data are thus often presented as odds ratios and not actuarial survival or stroke rates. All of this limits the range of TIA patients to whom the resultant natural history data can be applied. However, the prospective, blinded, meticulous methodology of most treatment trials provides high quality information of great value to clinicians managing TIA patients of similar etiology.

**Antiplatelet trials**

Among antiplatelet studies, two of the largest trials using placebo were conducted in Europe. Each included patients with TIA or minor ischemic stroke.

In the United Kingdom transient ischaemic attack (UK-TIA) aspirin trial, 2435 patients were randomized to aspirin 300 mg once daily, aspirin 600 mg twice daily, or placebo [72,73]. Patients were over 40, had suffered their stroke or TIA within 3 months of randomization, had not previously experienced a disabling stroke, had not suffered a myocardial infarction within 3 months, and were not ‘likely to experience adverse effects from aspirin’. Patients with cardioembolic mechanisms were included if they were not anticoagulated. Patients who ‘might have difficulty with follow up, might comply poorly, or had severe intercurrent nonvascular disease’ were excluded. In the European Stroke Prevention Study (ESPS) (I), 2500 patients were treated with aspirin plus dipyridamole or placebo and followed for 2 years [74,75]. Inclusion and exclusion criteria were similar to the UK-TIA aspirin trial but less explicit. Dropout rates in both trials were substantial. Among placebo patients,