Chagas disease is a neglected infectious disease in the tropics and an emerging health problem in Europe and the USA. In the past decade, a link has been recorded between ischaemic stroke and Trypanosoma cruzi infection in several epidemiological studies, and an increase in stroke prevalence is expected with the ageing of the population infected with T cruzi in Latin America. Heart failure, mural thrombus, left ventricular apical aneurysm, and several types of cardiac arrhythmias are associated with stroke in Chagas disease. Stroke could also be the first sign of Chagas disease in asymptomatic patients and those with mild systolic dysfunction, so patients with stroke who are from endemic regions should be screened for T cruzi infection. The most frequent stroke syndrome seen in patients with Chagas disease is partial anterior circulation infarction. Stroke recurrence has been estimated to occur in 20% of patients, and secondary prevention measures include chronic anticoagulation in cardioembolic chagasic stroke. So far, no studies have been done to assess the effect of chagasic stroke on vascular dementia.

Introduction
Chagas disease, or American trypanosomiasis, is a parasitic disease caused by the flagellate protozoan Trypanosoma cruzi. The Brazilian physician Carlos Chagas described the disease in 1909, and identified both the parasite and insect. However, the sylvatic cycle of American trypanosomiasis could have been well established when the earliest natives settled on the Andean coast 9000 years ago and became hosts for T cruzi. Kinetoplast DNA segments from T cruzi have been detected in tissue specimens from human mummies from northern Chile (Chinchorro culture), southern Peru, and central Brazil. Chagas disease is the third most common parasitic infection worldwide after malaria and schistosomiasis. It is an important public health problem in South America and an emerging disease in Europe and North America. In the past two decades, migration of thousands of paucisymptomatic patients from rural to urban areas in Latin America, and from endemic regions to developed countries has changed the epidemiology of the disease. Therefore, Chagas disease is an example of an infectious disease that is rapidly adapting in the era of globalisation.

Major complications occur in the chronic phase of disease, such as disability due to chronic cardiomyopathy and stroke. Chagas disease most affects people with low income and restricted access to medical treatment, presenting a heavy burden for patients and their families. Ischaemic stroke has been a neglected and unrecognised complication of Chagas disease for many years, but in the past decade several epidemiological studies have elucidated the clinical course of stroke in these patients. Improvements in serological and molecular techniques for diagnosis and in access to non-invasive methods, such as echocardiography and MRI, have helped to increase our understanding of the cerebrovascular complications of Chagas disease. Here, we review the methods for diagnosis, treatment, and prevention of stroke in Chagas disease.

Transmission of infection
Panel 1 shows the most common routes of transmission of T cruzi infection. Vector-borne transmission to human beings and other mammals is caused by haematophagous Triatominae bugs of the family Reduviidae. Although more than 130 different species of triatomines have been identified, four—Triatoma infestans, Rhodnius prolixus, Panstrongylus megistus, and Triatoma dimidiata—act as the main vectors for transmission. In the sylvatic cycle, the triatome defecates on the host while feeding on blood from the bite wound. The faeces are contaminated with trypanosome, which enters through the wound of the skin or mucous membranes. Several sylvatic vertebrates (eg, armadillo and raccoon) and domestic animals (mainly dogs and cats) are reservoirs for T cruzi. Poor people from rural communities in Central and South America are exposed to Triatominae bugs, which mainly infest holes and cracks in mud houses.

Transmission by blood transfusion is the second most common mechanism of infection: between 1980 and 1989, prevalence of T cruzi-infected blood in blood banks of selected Brazilian towns ranged from 2–9% (Sao Paulo, 1982; 57 000 cases) to 14.6% (Brasilia, 1984; 2413 cases). Congenital transmission affects 2–10% of babies born from infected mothers in endemic regions in northern Argentina and Bolivia. Premature labour and low birthweight are common complications, but the effect of congenitally transmitted disease on the development of infected children is still unknown. Oral transmission has been suspected in the past, and recently several outbreaks of acute Chagas disease were reported in Brazil and Venezuela after ingestion of contaminated juices and food, and acute trypanosomiasis was reported after ingestion of açai juice (Euterpa catinga) in the Brazilian states of Amazonas, Pará, Amapá, and Acre.
Epidemiology
Currently, around 100 million people live in geographical regions where Triatominae are detected. American trypanosomiasis is spread from southern Texas, Mexico, and Central America to Brazil, Venezuela, Colombia, and northern Argentina and northern Chile. About 8–14 million people have the chronic form of the disease. Two decades ago, more than 18 million people were infected. Today, 220 000 new cases and more than 14 000 deaths are reported yearly, and about a third of patients with T cruzi infection will develop chronic Chagas heart disease.6

Fever new cases of acute disease have been recorded since implementation of the Southern Cone Initiative.11 Brazil, Chile, and Uruguay have now been declared free of transmission by Triatoma infestans, and Guatemala free of Rhodnius prolixus.12–13 Compulsory screening for Chagas disease in blood banks has also contributed to increased infection control in some Latin American countries.14

American trypanosomiasis is no longer reported exclusively in rural regions. Rural to urban migration in many Latin American countries in the past 30 years has changed the traditional epidemiological pattern. Chagas disease is also an emerging infectious disease in developed countries because thousands of infected individuals, many of them asymptomatic, have emigrated from endemic countries.6 About 14 million people have moved from endemic countries to Europe, North America, Japan, and Australia in the past 20 years.15 In these cases, transmission via blood transfusion and from mother to child occur without the triatomine vector. An important concern is the selection of T cruzi lineages that are less dependent on vectors and better adapted to alternative routes of transmission.

T cruzi might cause a substantial disease burden in the USA. More than 300 000 Latin American immigrants with T cruzi infection could be living in the USA at present, with 30 000–45 000 cardiomyopathy cases and 300 congenital infections occurring yearly.21 Many chagasic cardiomyopathies might be misdiagnosed as primary dilated idiopathic cardiomyopathies in these non-endemic regions.22 In Europe, an increase in the number of people with T cruzi infection has been detected.23–25 Transmission from mother to child, and via transfusion and transplantation have accounted for all cases. The screening of blood supply for Chagas disease is now mandatory in the USA.26 Spain, and France.6 In Spain, a country that traditionally receives most immigrants from South America, T cruzi seroprevalence among blood donors from endemic regions is 0–6.2%, with the highest prevalence in Bolivian donors (10–25%).27 In an epidemiological study in Barcelona, 3.4% of 1350 Latin American pregnant women were infected, as were 7.3% of babies born from infected mothers.28

Chagas disease causes loss of an estimated 667 000 disability-adjusted life-years, and the disease burden, disability, and death mainly affect young and middle-aged people.26 Nevertheless, infection is highly prevalent in elderly people, possibly because the population infected with T cruzi in Latin America is ageing. Consequently, an increase in cerebrovascular complications of Chagas disease is expected in the coming decades.26 Many patients with Chagas disease do not know that they are infected. Data from an epidemiological study showed that in 42% of patients with Chagas disease who had had their first ischaemic stroke, infection was diagnosed after the occurrence of the stroke.27

Diagnosis
Phases of disease
American trypanosomiasis has two differentiated phases: acute and chronic. Most acute cases are asymptomatic, last for 6–12 weeks, and occur in childhood.16 Focal oedema is detected at the site of inoculation in some patients, and the appearance of unilateral orbital oedema is known as Romaña’s sign. Clinical acute Chagas disease can present with febrile syndrome, headache, myalgia, facial oedema, abdominal pain, exanthema, lymphadenopathy, and hepatosplenomegaly.29 Severe myocarditis and acute encephalitis can also occur.30 Most patients seem to recover a healthy state and enter into the indeterminate form of disease, in which the infected person is asymptomatic and no organ damage can be detected.31 Electrocardiography (ECG), chest radiography, and contrast radiography of the colon and oesophagus are normal; only serological studies are positive for Chagas disease.32 A round 30–40% of patients with T cruzi infection are expected to enter into the chronic form of disease. Signs of chronic infection can occur up to 30 years after initial infection. The most frequent chronic form of disease is chagasic cardiomyopathy, which is associated with heart failure, arrhythmias, sudden death, peripheral thromboembolism, and stroke.32 ECG findings include right bundle branch block (isolated, or associated with left anterior hemiblock), ventricular extrasystoles, abnormal Q waves, primary alteration of ventricular repolarisation, various degrees of atrioventricular block, sick sinus syndrome, and supraventricular tachyarrhythmias.34 Segmental cardiac fibrosis and dilatation with a tendency towards aneurysm formation, particularly in the apical region, are prominent features of the heart in infected individuals during the chronic phase. In at least 10–20% of patients, gastrointestinal disorders with increased diameter of the organ can occur.32 Megaoesophagus can result in chronic dysphagia, megacolon can provoke chronic constipation, and further complications are malnutrition and volvulus.35

Several pathogenic theories have been postulated to explain chronic cardiomyopathy in Chagas disease (panel 2).1,36–38 Parasite DNA has been detected in organ tissues with sensitive techniques such as PCR.39–41 Genotypic variation between T cruzi lineages from different geographical regions could explain the well known variability in virulence, susceptibility to the immune response of the host, tissue tropism, and clinical symptoms in Chagas disease.39
Diagnostic techniques
Parasitological studies (thick smears of peripheral blood and cerebrospinal fluid smears, microhaematocrit, and other concentration techniques) allow direct visualisation of T cruzi trypomastigotes, and are useful to confirm acute cases and reactivation in immunosuppressed patients. Direct visualisation of T cruzi is difficult in the chronic phase because of low parasitaemia. Only haemoculture and xenodiagnosis can be used to directly detect T cruzi infections in the chronic phase, but these techniques are not useful in clinical practice. In xenodiagnosis, a presumably infected individual is exposed to an uninfected, laboratory-bred vector and the vector is then examined for the presence of T cruzi. Haemoculture is not used in clinical practice owing to technical requirements and low growth of T cruzi, and because the currently available PCR techniques are easier to use.

Diagnosis of chronic T cruzi infection relies on serological methods. A positive antibody titre indicates that infection has been present at some point but is not necessarily current, and serological studies cannot differentiate between acute, indeterminate, and chronic phases. Individuals are judged to be infected when they have a positive result from at least two serological techniques that use different antigens. A third technique should be used in cases of discrepancies. Enzyme immunoassay is better than other screening assays (sensitivity 97·6–100%; specificity 96·5–99·6%), such as haemagglutination (88%; 59–76%). However, confirmatory assays have good sensitivity and specificity: indirect immunofluorescence (sensitivity 98·2%; specificity 98·0%), western blot (100%; 97·3%), radioimmuno-precipitation assay (100%; 97·3%), and recombinant immunoblot (98·2%; 99·6%).

PCR-based assays are useful to detect low concentrations of T cruzi DNA in blood samples from patients with Chagas disease, and to examine tissue samples from infected organ donors. Although PCR of blood might not be useful as a routine test in adults for practical reasons and because PCR validation studies in adults with Chagas disease are yet to be done, it can be used to diagnose suspected cases of congenital Chagas disease, or for early diagnosis of reactivation in immunosuppressed patients (eg, in patients with autoimmune diseases, after transplantation in patients receiving organs from donors with Chagas disease, or in patients with Chagas disease who are receiving organs). PCR sensitivity can vary between endemic regions because of differences in genetic strains that affect parasitaemia, the phase of disease (acute or chronic), and the primers and method used. In a comparison of two diagnostic techniques in patients with chronic Chagas disease, PCR had high specificity (100%) and moderate sensitivity (70–75%), and TESA-blot, a western-blot technique that uses trypomastigote excreted-secreted antigen (TESA), had a sensitivity of 100% and a specificity of 99·2%.

Epidemiology of chagasic stroke
Cerebral infarctions in Chagas disease have been described in autopsy series, case-control studies, clinical case series, and cohort studies of patients with the indeterminate form of Chagas disease, or, more often, with advanced chronic heart disease. Necropsy studies are usually retrospective or cross-sectional, and most have assessed patients with severe or advanced cardiomyopathy. No primary pathological studies have focused on patients with chagasic stroke.

Clinical case series and epidemiological studies have usually had a small sample size of less than 150 patients with chagasic stroke, with differing geographical regions, hospital settings, and recruitment and inclusion criteria. Additionally, several studies have not used appropriate definitions and classifications to assess stroke subtypes, and no differentiation has been established between indeterminate and chronic forms of disease. Only one prospective study of stroke patients—94 with Chagas disease and 150 without—involved a systematic work-up diagnosis for ischaemic stroke. Patients with stroke underwent a protocol including brain MRI or CT scan, carotid echo-doppler, transcranial doppler, transthoracic or transoesophageal echocardiogram, or both, and thrombophilia studies.

In retrospective autopsy series of patients with Chagas disease and chronic heart failure, 18–20% had cerebral infarctions, and half had an association between cerebral infarction and death. Findings from necropsy studies show that the frequency of haemorrhagic stroke is lower in patients with Chagas disease than in those without. However, these studies recruited patients with severe or advanced cardiomyopathy.

The natural history of stroke in people with T cruzi infection is not well understood. Data from the Bambuí study, a population-based study of the association between T cruzi infection and cognitive impairment in old age, showed that about 5·4% of 545 Brazilian people with Chagas disease had had an ischaemic stroke. This prevalence of stroke is higher than in the general Brazilian population.

Panel 2: Pathogenic factors in chronic Chagas disease

<table>
<thead>
<tr>
<th>Direct tissue damage by Trypanosoma cruzi</th>
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<tbody>
<tr>
<td>• Parasite persistence</td>
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<td>• Inflammation</td>
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<tr>
<th>Neurogenic impairment</th>
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<tbody>
<tr>
<td>• Parasympathetic and sympathetic dysfunction</td>
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<table>
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<tr>
<th>Microvascular impairment</th>
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<tbody>
<tr>
<td>• Alterations in coronary microcirculation</td>
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<tr>
<td>• Focal vascular constriction, microaneurysm formation, dilatation and proliferation of microvessels</td>
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<table>
<thead>
<tr>
<th>Autoimmune processes</th>
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<tbody>
<tr>
<td>• Factors associated with host’s immune system</td>
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<tr>
<td>• Lymphomononuclear infiltration, cross-reactive antibodies</td>
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population (2.3–3.9%; analyses adjusted for age and sex). However, the population in the Bambuí study might not have been representative of all patients with Chagas disease because of a selection bias towards elderly patients. Additionally, data were based on interviews to assess lifetime history of stroke, with no clinical evaluation or assessment with CT or MRI. Reports from prospective hospital-based case-control studies have shown that about 20% of patients with stroke who were consecutively admitted to hospital in endemic regions of central Brazil were seropositive for *T cruzi* infection.

A few studies have assessed the risk of ischaemic stroke in patients with chronic heart disease associated with Chagas disease. In a cross-sectional study done in a cardiology outpatient clinic in Bahia, Brazil, ischaemic stroke was significantly more frequent in patients with Chagas disease than in those with embolic cardiomyopathies unrelated to Chagas disease (15.0% vs 6.3%; *p*=0.01). However, only 10% of 305 patients assessed had a stroke, investigators did not do complete work-up diagnosis of stroke or classification of stroke subtype, and no information was provided about the similarity of cardiac diseases between study groups.

In the past 20 years, Chagas disease has been associated with symptomatic cerebrovascular disease in several epidemiological studies. Results from a case-control study in eastern Colombia showed that *T cruzi* infection was significantly more frequent in patients with ischaemic stroke (n=88 patients) than in control patients (n=102; 25% vs 2%; odds ratio 16.2, 95% CI 3.6–71.4). The association remained significant after removal of seropositive patients with cardiac abnormalities from the multivariate analysis (*p*<0.05). In a case-control study in Brazil, *T cruzi* infection was significantly more common in 101 consecutive cases of acute stroke than in 100 cases of acute coronary syndrome (14% vs 2%; *p*=0.002). However, no systematic stroke subtype classification was done in either of these studies. More than 60% of stroke patients with Chagas disease who live in endemic regions have a positive family history of Chagas disease, which is substantially higher than in stroke patients without Chagas disease (16%). Social variables associated with chagasic stroke are having family members with Chagas disease and living in a mud-brick house during childhood.

Few data are available on the cumulative risk of stroke in people with *T cruzi* infection. In a cohort with mild chagasic cardiomyopathy, about 1.2% had ischaemic stroke during the first year of follow-up.

Follow-up of 213 patients with Chagas disease and left ventricular systolic dysfunction for a mean of 36 months showed an overall incidence of ischaemic stroke of 2.7 events per 100 patient-years. These studies were done in cardiology reference centres, not in the community, which could lead to selection bias. Nevertheless, stroke could be the first sign of Chagas disease in patients with asymptomatic or chronic disease, irrespective of systolic dysfunction or presence of cardiac arrhythmias. Patients with Chagas disease but without associated vascular risk factors or clinical evidence of heart failure could also be at risk of stroke.

Chronic heart disease and gastrointestinal forms of disease can coexist in patients with chagasic stroke (figure 1). A chronic chagasic intestinal form has been reported in 20% of patients with chagasic stroke (8% with megaoesophagus, 8% with megacolon, and 4% with both). Additionally, several systemic thromboembolic events can occur simultaneously. Coexistence of cardioembolic stroke and ischaemic small bowel infarction caused by occlusion of the mesenteric artery has been described in Chagas disease. Other types of peripheral embolism could affect the lungs, kidney, spleen, and liver.

**Pathogenesis and clinical findings in chagasic stroke**

**Cardioembolism**

Panel 3 shows known risk factors for cardioembolic stroke in Chagas disease. Chagasic cardiomyopathy is independently associated with ischaemic stroke. Chagas chronic heart disease is characterised by the presence of...
congestive heart failure, several types of arrhythmias (atrial fibrillation, intraventricular conduction defects, and severe atrio-ventricular block), sudden cardiac death, and systemic thromboembolism. The main risk factors associated with chagasic stroke include cardiac apical aneurysm, arrhythmias, mural thrombus, and left ventricular dysfunction. Other independent risk factors for stroke are left ventricular ejection fraction and left atrial volume (corrected for body surface area).

About 70% of patients with chagasic stroke have ECG abnormalities, such as right bundle branch block (23·0–35·1%), left fascicular block (17·0%), atrial fibrillation (14·9%), and pacemaker rhythm (9·4%). The risk of intraventricular conduction as a source of embolism in Chagas disease needs further assessment. In patients with chagasic stroke, the most frequent findings of transoesophageal echocardiography are left ventricular dysfunction (65%), apical aneurysm (37–40%), left ventricular dilatation (23%), and mural thrombus (12%). The apical region of the left ventricle is most commonly affected by aneurysm and mural thrombus. In echocardiographic studies, apical aneurysm occurs in 20% of patients with chagasic chronic cardiomyopathy, which is much more frequent than in other aetiologies of cardiomyopathy (eg, postschaemical, hypertensive), but there are no echocardiographic criteria to differentiate between causes of cardiomyopathy. In these cases, diagnosis depends on serological studies.

Stroke patients with Chagas disease are significantly younger than those without (56·3 vs 61·6 years; p=0·0002). Female sex has also been associated with increased risk of chagasic stroke after adjustment for covariables, whereas low survival in men has been associated with chronic chagasic cardiomyopathy. However, whether female sex is a risk factor for Chagas disease or for stroke in patients with Chagas disease needs to be established. Findings from the Framingham study indicated a survival advantage for women with heart failure. Lengthened survival in women with chagasic chronic cardiomyopathy could put them at increased risk of embolic stroke, but survival studies are needed to investigate this hypothesis.

Classic vascular risk factors, such as hypertension, diabetes mellitus, and smoking, are less common in stroke patients with Chagas disease than in those without, according to a cross-sectional study (n=136 vs n=239). Hypertension is the most common vascular risk factor found in patients with the indeterminate form of Chagas disease. In case-control studies of stroke patients, presence of Chagas disease is also associated with increased frequency of congestive heart failure (27·7% vs 2·7%) and atrial fibrillation (13·8% vs 5·3%). However, prevalence of vascular risk factors might vary in urban and rural regions of South America, and selection bias could occur in large countries (eg, Brazil) with a wide ethnic, geographical, and cultural diversity.

Ageing of the population infected with T cruzi is an additional risk for cerebrovascular complications. Patients could also have mixed types of chronic cardiomyopathy after adaptation to lifestyles in developed countries. The increased proportion of patients with Chagas disease who are smokers, and have diabetes, obesity, and sedentary lifestyles could change the natural history of chagasic cardiomyopathy and increase the risk of stroke.

Other stroke subtypes

Not all ischaemic chagasic strokes are caused by cardioembolism. Other causes could be large vessel atherothrombosis (8–5% of patients) and small vessel disease (9·6%). Haemodynamically significant internal carotid artery stenosis can be observed in 1–1% of patients. Small atherosclerotic plaques are usually found in a third of patients with chagasic stroke. Such disorders are probably caused by the presence of classic vascular risk factors, mainly hypertension for small vessel disease and smoking for large artery occlusion. Neither direct involvement of the pathogenic organism, T cruzi, nor inflammation in arterial walls has been reported in patients with acute ischaemic stroke and chronic Chagas disease. Some evidence suggests that T cruzi damages both heart and vascular smooth muscle in acute infection in mice, and causes generalised vasculitis, but the long-term effect of acute vasculopathy on small vessels of the brain is unknown. Mice with acute Chagas disease have presented with focal formation of ischaemic microaneurysms and focal vascular constriction, but pathological studies of vessels of the brain have not replicated these findings in patients with chronic Chagas disease. In around 20–25% of patients with stroke and T cruzi infection, the aetiology of ischaemic stroke is classified as cryptogenic. About a third of patients with chagasic stroke of undetermined cause had normal echocardiograms and carotid echodoppler, and no associated vascular risk factors.

Thrombophilia

Procoagulant factors do not seem to be a risk factor for cardioembolic stroke in Chagas disease. In a case-control
Although fairly infrequent, posterior circulation infarctions and top-of-the-basilar syndrome can provoke severe debilitating strokes. Lacunar syndromes usually occur in an increased proportion of elderly patients with \textit{T cruzi} infection. Embolism is most common in the middle cerebral artery, occurring in 80–90% of cases\(^6\) (figure 2A). Isolated infarctions in the internal capsule and centrum semiovale account for 7–5% of the ischaemic infarctions, according to brain MRI studies. Single infarction of the pons or cerebellum occurs in less than 5% of patients with chagasic stroke\(^6\) (figure 2B).

Seizures sometimes occur at stroke onset, and epilepsy is quite a frequent complication after chagasic stroke. Chronic vascular epilepsy, characterised by secondary generalised seizures, has been reported in around 20% of patients surviving chagasic stroke, whereas around 10% of stroke patients without Chagas disease have seizures.\(^6\) The effect of uncontrolled seizures on cognition and disability in Chagas disease is unknown. No prospective epidemiological studies have addressed the risk of acute seizures and their recurrence in acute chagasic stroke.

**Treatment**

**\textit{T cruzi} infection**

The trypanocidal drugs benznidazole, a nitroimidazole derivative, and nifurtimox can be used to treat \textit{T cruzi} infection. Treatment cures 60–85% of children,\(^7,7\) and close to 100% of infants.\(^8\) However, the effectiveness of benznidazole and nifurtimox in chronic Chagas disease is an unsolved problem.\(^9\) Side-effects are common with these drugs (table).\(^7,7\) In patients treated with benznidazole, about a quarter develop dermatitis and 10% develop acute pneumonitis.\(^7,8\) Around half of nifurtimox-treated patients have gastrointestinal disorders.\(^7,7\) Children treated with these trypanocidal drugs have fewer adverse effects than do adults.

Trypanocidal drugs should be used to treat acute trypanosomiasis, congenital infection, and chronic infection in patients younger than 18 years, people affected by accidents in laboratories, and disease reactivation in patients with HIV infection or immunosuppression. Benznidazole treatment prevented development of severe chronic cardiomyopathy in a mouse model of chronic Chagas disease, and led to lower concentrations of antibodies against \textit{T cruzi} antigens (epimastigote extract, P2β, and trans-sialidase) than in serum of untreated mice.\(^8\) In human beings, benznidazole treatment reduces the proportion of patients with positive xenodiagnosis\(^9\) and increases the likelihood of negative seroconversion\(^2\) and negative real-time PCR findings.\(^3\) Data from a non-randomised unblinded trial suggest that oral benznidazole (5 mg/kg of bodyweight per day) for 30 days could slow the progression of chagasic cardiomyopathy in adults, and increase conversion to negative serology for patients presenting with non-acute disease and no heart failure.

### Panel 4: Indications for Chagas disease in patients with ischaemic stroke

<table>
<thead>
<tr>
<th>Indication</th>
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<tbody>
<tr>
<td>Patient from endemic region in South America</td>
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<tr>
<td>Family members with Chagas disease</td>
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<tr>
<td>Immigrants in Europe or North America from endemic Latin American countries</td>
</tr>
<tr>
<td>Contact with insect vector (\textit{Triatoma spp}) during infancy</td>
</tr>
<tr>
<td>Past history of living in mud houses in endemic areas during infancy</td>
</tr>
<tr>
<td>Past history of previous stroke or vascular epilepsy(^a)</td>
</tr>
<tr>
<td>Past history of chronic idiopathic dilated cardiomyopathy</td>
</tr>
<tr>
<td>Detection of megaesophagus or megacolon, or both</td>
</tr>
<tr>
<td>Clinical symptoms of heart disease or cardiac arrhythmia, or both(^b)</td>
</tr>
<tr>
<td>Presence of right bundle branch block on ECG(^a)</td>
</tr>
<tr>
<td>Presence of advanced atrioventricular block on ECG(^a)</td>
</tr>
<tr>
<td>Detection of apical aneurysm on echocardiogram without history or evidence of myocardial infarction</td>
</tr>
<tr>
<td>Several cortical strokes on brain CT scan(^a)</td>
</tr>
<tr>
<td>Partial or total anterior circulation infarctions, or both, on brain CT scan(^a)</td>
</tr>
</tbody>
</table>

\(\text{ECG=electrocardiography.} \quad \text{\textsuperscript{\(a\)}} \text{Unspecific clues in non-endemic areas.}\)

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**Clinical signs and symptoms**

No specific signs or neurological symptoms can distinguish chagasic stroke from other causes of cardioembolic stroke. Panel 4 lists indications for Chagas disease in patients with ischaemic stroke. In chagasic stroke, previous silent infarctions have been detected (with CT scan or brain MRI) in around 18% of patients, and, as expected in cardioembolic stroke, partial and total anterior circulation infarctions occur in most patients (about 85%).\(^7,7\) Cerebral infarctions predominate in frontal, parietal, and temporal lobes, and in the basal ganglia. Stroke onset is usually accompanied by decreased consciousness, and by severe focal cortical, motor, and visual deficits (aphasia, hemineglect, hemiplegia, tonic gaze deviation, and hemianopsia).
The primary outcome of this study was disease progression or death, and secondary outcomes included new abnormalities on ECG. Whether reduced parasite load can improve the clinical consequences of disease is unknown. The multicentre BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial is underway to assess the effect of benznidazole on the clinical progression of chronic cardiomyopathy in patients with Chagas disease.

Even though scientific evidence to support treatment of chronic *T cruzi* infection is insufficient, in practice, several experts recommend treatment of adults (<50 years) without advanced cardiomyopathy. For adults older than 50 years, the risk of toxic effects from drugs might be increased so trypanocidal treatment should be optional in view of the lack of certainty of benefit, long-term course needed, and frequent adverse effects. Moreover, the high frequency of adverse effects and the slow progression from indeterminate to definite form support withholding of treatment for chronic disease. Consequently, the decision to treat chronic disease is based more on the preference of the clinician than on evidence-based recommendations, but findings from the BENEFIT study will contribute towards future recommendations.

No evidence exists about the use of trypanocidal drugs in patients with chagasic stroke, particularly since most cases of chagasic stroke occur in chronic disease. Future studies are needed to determine whether trypanocidal treatment is beneficial in young and middle-aged patients with Chagas disease who have had an ischaemic stroke but have no vascular risk factors. These patients could have severe disability and, on some occasions, other associated comorbidities, so careful clinical monitoring is needed. Additionally, in chagasic cardiomyopathy associated with stroke, one of the main limitations to assessment of the efficacy of trypanocidal drugs is the need for long-term follow-up, because seronegative conversion can be achieved several years after treatment. Early markers for cure or progression of Chagas disease after treatment are lacking.

**Ischaemic stroke**

In stroke patients with *T cruzi* infection, treatment of acute stroke and secondary prevention measures should be done according to stroke guidelines. Reports on the use of thrombolytic treatment in acute chagasic stroke are scarce: successful thrombolysis in only two patients with cardioembolic stroke secondary to Chagas disease have been noted in case-report series. No studies have assessed the potential risk of thrombolytic therapy in Chagas disease.

Since 1995, thrombolytic treatment has been increasingly used in acute ischaemic stroke. However, patients with high risk of cardiac thrombus (eg, after acute myocardial infarction) have been excluded from the major multicentre studies. Recurrent stroke after thrombolysis in patients with pre-existing intracardiac thrombus has been reported, which calls into question whether risk of treatment exceeds benefit in this population. About 12% of patients with chagasic stroke have a left ventricular mural thrombus. Although the use of tissue plasminogen activator is not contraindicated in patients with chagasic stroke and mural thrombus, some investigators recommend that in patients with Chagas disease, left ventricular thrombus should be ruled out by echocardiography before starting thrombolytic treatment. The risk of recurrent stroke in such patients receiving tissue plasminogen activator is probably low, but needs further study. Moreover, the safety of thrombolytic treatment in patients with Chagas disease who have a stroke and an apical aneurysm is unknown and needs further study.

Chagasic stroke affects large arteries, and clinically provokes large ischaemic infarctions and severe impairment and disability. A multidisciplinary approach is needed for long-term treatment of such patients after stroke: neurologists, gastroenterologists, cardiologists, cardiac surgeons, physiotherapists, and primary care physicians should form part of an integrated team. Realistic rehabilitation goals need to be set, and secondary prevention measures should be undertaken in view of the fact that in developing countries, many patients with chagasic stroke live in rural regions and might have restricted access to health care.

**Stroke recurrence and predictors of death**

Studies have been done to assess predictors of death in chronic chagasic cardiomyopathy, but not cardiovascular mortality in chagasic stroke. Pulmonary and cerebral embolism could be the third most common cause of death in Chagas disease after fatal arrhythmias and progressive heart failure. Independent predictors of death in chronic...
cardiomyopathy include New York Heart Association class III or IV, cardiomegaly on chest radiography, segmental or global wall motion abnormalities on 2D echocardiography, non-sustained ventricular tachycardia on 24-h Holter, low QRS voltage on ECG, and male sex.91 These factors might non-sustained ventricular tachycardia on 24-h Holter, low global wall motion abnormalities on 2D echocardiography, III or IV, cardiomegaly on chest radiography, segmental or cardiomyopathy include New York Heart Association class III or IV, cardiomegaly on chest radiography, segmental or global wall motion abnormalities on 2D echocardiography, non-sustained ventricular tachycardia on 24-h Holter, low QRS voltage on ECG, and male sex.91 These factors might also increase the risk of vascular mortality in chagasic stroke, but no studies have focused on predictors of death in acute ischaemic chagasic stroke.

For patients with chagasic stroke, a history of ischaemic stroke has been recorded in 20–22% of cases, with a new vascular territory affected in 80% of cases.60 Further stroke has been recorded in 20–22% of cases, with a new vascular territory affected in 80% of cases.60 Further studies of stroke recurrence in Chagas disease are needed to prove this link.52

Conclusions and future directions
In a study in central Brazil, 80 stroke patients with Chagas disease and 140 without were interviewed with a standardised questionnaire to assess awareness of Chagas disease as a risk factor for stroke.27 Most respondents (95%) were not aware of the risk of stroke, and patients with Chagas disease had a lower awareness than patients without, although this difference did not reach statistical significance (2.5 vs 7.1%; p=0.22). Educational campaigns about the high risk of stroke in Chagas disease are therefore needed in schools and public health centres.

Chagas disease is an independent risk factor for ischaemic stroke. Cardioembolism is the main cause, but cryptoembolic stroke and small vessel stroke occur with substantially increased frequency in indeterminate Chagas disease and in patients with mild chronic heart disease related to Chagas disease. A careful work-up diagnosis of stroke is needed in these patients, and the presence of left ventricular segmental lesions (apical aneurysm and mural thrombus) should be excluded.

Early diagnosis and secondary prevention measures should be encouraged in chagasic stroke. Patients with ischaemic cardioembolic or cryptogenic stroke should be screened for T cruzi infection if they reside in or have emigrated from endemic regions. Clinical trials are needed to assess the efficacy of long-term oral anticoagulation in patients with Chagas disease who have had an ischaemic stroke or for primary prevention of stroke.95,96

Search strategy and selection criteria
We searched PubMed (January, 1970, to January, 2010) for references and reports using the search terms "Chagas disease", "stroke", and "American trypanosomiasis". We also identified reports and journals that were not cited in PubMed from searches of our own files. The reference lists of selected articles were searched for further relevant reports. Articles published in English, Spanish, and Portuguese were reviewed.

<table>
<thead>
<tr>
<th>CNS side-effects</th>
<th>Benznidazole</th>
<th>Nifurtimox</th>
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</thead>
<tbody>
<tr>
<td>Sleep disorders (eg, insomnia)</td>
<td>10-20%</td>
<td>10-13%</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>27%</td>
<td>8%</td>
</tr>
<tr>
<td>Acute polyneuritis</td>
<td>5-10%</td>
<td>Rare</td>
</tr>
<tr>
<td>Headache</td>
<td>2-8%</td>
<td>10-28%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>–</td>
<td>12%</td>
</tr>
<tr>
<td>Seizures</td>
<td>–</td>
<td>Rare (&lt;1%)</td>
</tr>
<tr>
<td>Ataxia or nystagmus</td>
<td>–</td>
<td>Rare (&lt;1%)</td>
</tr>
<tr>
<td>Disorientation or forgetfulness</td>
<td>–</td>
<td>10%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>–</td>
<td>1-2%</td>
</tr>
<tr>
<td>Mood changes or irritability</td>
<td>–</td>
<td>Rare (&lt;1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin disorders</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Myalgia or arthralgia</td>
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<tr>
<td>Increase in transaminases</td>
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<tr>
<td>Pruritus</td>
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<td>Oedema</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Bone marrow suppression</td>
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<tr>
<td>Leucopenia</td>
</tr>
</tbody>
</table>

Data are percentage of patients. – zero or not reported. *Rash and exfoliative dermatitis. †Skin rash.
References


8 Schmunis GA. Trypanosoma cruzi, the etiologic agent of Chagas disease: status in the blood supply in endemic and non endemic countries. Transfusion 1991; 31: 547–57.


