

Intravenous Immunoglobulin in Acute Rheumatic Fever

A Randomized Controlled Trial

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Background—Acute rheumatic fever (ARF) remains the leading cause of acquired heart disease in children worldwide. No therapeutic agent has been shown to alter the clinical outcome of the acute illness. Immunological mechanisms appear to be involved in the pathogenesis of ARF. Intravenous immunoglobulin (IVIG), a proven immunomodulator, may benefit cardiac conditions of an autoimmune nature. We investigated whether IVIG modified the natural history of ARF by reducing the extent and severity of carditis.

Methods and Results—This prospective, double-blind, randomized, placebo-controlled trial evaluated IVIG in patients with a first episode of rheumatic fever, stratifying patients by the presence and severity of carditis before randomization. Patients were randomly allocated to receive 1 g/kg IVIG on days 1 and 2 and 0.4 g/kg on days 14 and 28, or they received a placebo infusion. Clinical, laboratory, and echocardiographic evaluation was performed at 0, 2, 4, 6, 26, and 52 weeks. Fifty-nine patients were treated, of whom 39 had carditis (including 4 subclinical) and/or migratory polyarthritis (n=39). There was no difference between groups in the rate of normalization of the erythrocyte sedimentation rate or acute-phase proteins at the 6-week follow-up. On echocardiography, 59% in the IVIG group and 69% in the placebo group had carditis at baseline. There was no significant difference in the cardiac outcome, including the proportion of valves involved, or in the severity of valvar regurgitation at 1 year. At 1 year, 41% of the IVIG and 50% of the placebo group had carditis.

Conclusions—IVIG did not alter the natural history of ARF, with no detectable difference in the clinical, laboratory, or echocardiographic parameters of the disease process during the subsequent 12 months. (*Circulation*. 2001;103:401-406.)

Key Words: rheumatic heart disease ■ proteins ■ echocardiography ■ immune system

Acute rheumatic fever (ARF) continues to produce significant cardiac morbidity and mortality in young people in the developing world, where it remains the leading cause of acquired heart disease.^{1,2} In New Zealand, the incidence of ARF is 2.5 per 100 000 population, which compares with an incidence of 0.1 per 100 000 population in the United States.³ The incidence of 50 to 70 per 100 000 in Maori and Pacific Island children between 5 and 15 years of age is comparable to that seen in developing countries.⁴

Although an acute episode of rheumatic fever is preceded by a streptococcal throat infection, the mechanism that triggers ARF has not been elucidated.^{5,6} There is no proven pharmacological treatment that alters the natural history of rheumatic carditis, although corticosteroids and aspirin are frequently administered. Recent work has indicated that intravenous immunoglobulin (IVIG) may be of benefit in immune-mediated cardiac disorders.^{7,8} This is seen particularly in Kawasaki disease, in which the use of high-dose IVIG markedly reduces the prevalence of coronary artery abnormalities.⁹

We present the results of a randomized, placebo-controlled trial of IVIG as an acute intervention in patients with ARF to determine whether there was a reduction in the extent and severity of carditis, more rapid resolution of inflammatory activity, or decreased chronic morbidity.

Methods

All patients admitted with a diagnosis of a first episode of ARF that fulfilled the revised Jones criteria (1965¹⁰) were eligible for enrollment in this study. The updated 1992 Jones criteria¹¹ were published after initiation of this study, but all patients met these criteria also. Approval was obtained from the Auckland Hospital Board Ethics Committee, and all patients or their parents gave written consent for participation in the study. The first infusion of IVIG or placebo was begun within 72 hours of admission to hospital or as soon as possible after the diagnosis of ARF could be made with high probability. An initial diagnostic evaluation consisted of a full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein, streptococcal serology, anti-nuclear antibodies, rheumatoid factor, urea and electrolytes, liver function tests, hepatitis serology, Epstein-Barr virus serology, rubella serology, mycoplasma serology, throat swab, blood

Received May 3, 2000; revision received August 22, 2000; accepted August 23, 2000.

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cultures, midstream urine, ECG, chest x-ray, and detailed echocardiography.

The study was designed as a prospective, randomized, double-blind, placebo-controlled trial of IVIG. Randomization was by small-group random-number allocation. Exclusion criteria included patients with an ESR of <30 mm/h, a past history of rheumatic fever, IgA deficiency, chorea alone, evidence of marked valve thickening, or other evidence of chronic valvulitis on echocardiography. The patient, family, and cardiologists were unaware of the nature of the infusion being administered. Patients were stratified by the presence and severity of carditis before randomization. Each patient received an infusion of either IVIG or placebo (4% dextrose, 0.18% normal saline) at a dose of 1 g/kg on days 0 and 1 (maximum, 60 g) and then 0.4 mg/kg on days 14 and 28. Full assessments were made before the infusion. The IVIG preparation used (Intragam) was obtained from Commonwealth Serum Laboratories. This product is made by cold ethanol fractionation of human plasma and adjusted to a pH of 4. Human plasma was obtained from voluntary donations in New Zealand.

All patients received standard care for children with ARF. This consists of bed/chair rest in hospital for 2 weeks, oral penicillin for 2 weeks or until discharge, and then 4 weekly administrations of intramuscular benzathine (long-acting) penicillin. Salicylates were used as required for symptomatic relief of arthritis but were not prescribed routinely. Cardiac drugs were administered as required. Corticosteroids were not used. Patients with carditis remained on bed/chair rest in hospital until the ESR was <30 mm/h. Patients without carditis were discharged at 2 weeks on restricted activity.

Clinical, laboratory, and cardiac evaluation was performed at 0, 2, 4, 6, 26, and 52 weeks. Initial clinical assessment consisted of daily measurements of heart rate (awake and sleeping), temperature, joint involvement, and presence or absence of rash, chorea, or nodules. The blood parameters assessed weekly included ESR, C-reactive protein, and streptococcal serology for 6 weeks or until discharge if this was longer. Isolates of group A streptococcus grown from throat cultures were sent for M typing.

The end points assessed in this study were time to resolution of inflammation with assessment of time for the ESR to drop to ≤ 30 mm/h, time to quiescence of disease activity (joint symptoms) assessed clinically, and the difference in the frequency and severity of cardiac disease at each evaluation time point.

Cardiac evaluation consisted of assessment by standard clinical and echocardiographic criteria,¹² separately recorded for mitral, aortic, tricuspid, and pulmonary regurgitation, with the overall grade determined by echocardiography. Grades for valvar regurgitation were as follows: nil (including physiological or trivial valvar regurgitation),^{13,14} mild (including subclinical but pathological regurgitation),¹⁵⁻¹⁸ moderate, and severe.^{12,19} The minimal criteria to allow a diagnosis of pathological regurgitation included a substantial color jet seen in 2 planes extending well beyond the valve leaflets with continuous-wave or pulsed Doppler holodiastolic (aortic regurgitation) or holosystolic (mitral regurgitation) with well-defined, high-velocity spectral envelope.¹⁶ Mitral regurgitation was considered moderate if there was a broad high-intensity proximal jet filling half the left atrium or a lesser volume high-intensity jet producing prominent blunting of pulmonary venous inflow. Abnormal regurgitant color and Doppler flow patterns in pulmonary veins were a prerequisite for severe mitral regurgitation. Aortic regurgitation was considered moderate if the diameter of the regurgitant jet was 15% to 30% of the diameter of the left ventricular outflow tract with flow reversal in upper descending aorta.¹⁹ Reversal in lower descending aorta was required for severe regurgitation. Overall, carditis was considered present when there was echocardiographic mild or greater left heart valvulitis.¹⁶ Clinical carditis was considered present when there was a diagnostic murmur. Although diffuse and focal thickening of the mitral valve have been described in ARF,²⁰ we have not attempted to include such observations in our assessment. Isolated pulmonary or tricuspid regurgitation in the absence of left heart valvulitis was not considered evidence of carditis. One of 2 pediatric cardiologists (N.J.W., J.M.N.), both experienced in the assessment of children with rheumatic carditis, directly supervised the echocardi-

TABLE 1. Characteristics and Clinical Findings

	IVIG (n=27)	Placebo (n=32)	P
Mean age, y	11.2 \pm 2	11 \pm 3	NS
Sex, M/F	14/13	19/13	NS
Race, Maori/Pacific Islander	13/14	9/23	NS
Symptoms before admission, d	8 \pm 9	12 \pm 16	NS
Arthritis, d	2.9 \pm 2	3.7 \pm 6	NS
Salicylate use, d	17 \pm 16	20 \pm 19	NS

graphic studies, with particular attention paid to color gain consistency and standardization of views. All studies were recorded on Hewlett-Packard Sonos 1000 or 1500 echocardiographic machines with a full range of transducers. ECGs were recorded at each evaluation, but a chest radiograph was performed only at baseline and the 6-month follow-up.

Statistical Analysis

Continuous variables were compared by use of unpaired *t* tests (modified if the *F* test showed the variances were unequal) with allowance made for multiple comparisons by the Bonferroni adjustment. The χ^2 test was used for comparison of binary data with continuity correction.

Results

Sixty-two patients were enrolled in the study, but 1 patient withdrew when an alternative diagnosis was made. Twenty-nine received IVIG and 32 received placebo between March 1992 and October 1995. One patient with carditis withdrew from the study after the first week (parental choice), and another with carditis withdrew after 6 months (emigration). Both of these patients had been randomized to the IVIG group. Follow-up to 12 months was completed in the remaining 59 patients who are included in this report.

There was no difference in basic demographics between the 2 groups at enrollment (Table 1). All were indigenous Maori (37%) or Pacific Island New Zealanders (63%), the latter predominantly of Samoan ethnicity. Thirty-nine patients had migratory polyarthritis, 35 had clinical carditis, and 4 had subclinical carditis at diagnosis (Table 2). There were 2 patients with pericarditis in each group. Eight patients without carditis on admission developed evidence of carditis 2 to 6 weeks later. Four of these developed subclinical carditis only, and 4 developed clinical carditis.

TABLE 2. Major and Minor Criteria at Diagnosis

	IVIG (n=27)	Placebo (n=32)	P
Carditis	17	22	NS
Arthritis	19	20	NS
Chorea	0	2	NS
Erythema marginatum	0	1	NS
Subcutaneous nodules	0	1	NS
Fever ($\geq 38^\circ\text{C}$)	18	13	NS
Prolonged PR interval	20	19	NS
Arthralgia	22	27	NS
Raised ESR	27	32	NS

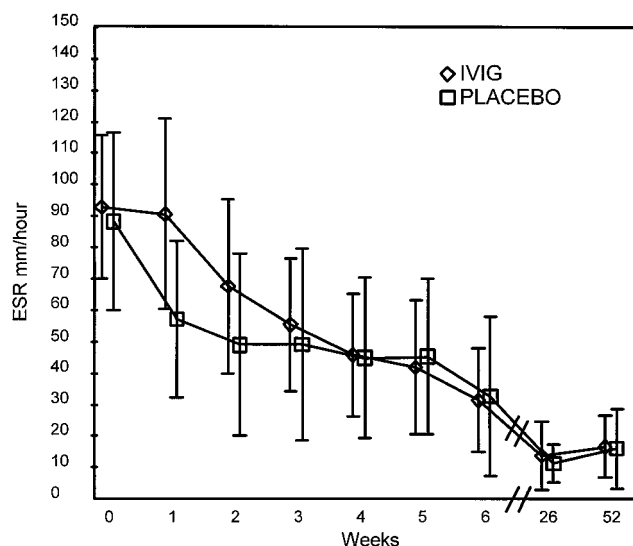


Figure 1. ESR measurements (mean and SD) in 2 groups. There were no differences in ESR level between the 2 groups at 6 weeks. Significant difference was noted at 1 and 2 weeks, with ESR result significantly higher in IVIG group. This effect was believed to be due to IVIG.

Twenty-two patients had arthritis as their only major criterion, 16 had carditis alone, 1 had arthritis with subcutaneous nodules, 2 had carditis and chorea, and 1 had carditis and erythema marginatum. By definition, no patient had a past history of rheumatic fever. Minor thickening of the mitral valve in 4 patients was attributed to acute rather than chronic rheumatic fever. A family history of rheumatic fever was present in 22 patients (37%; 14 IVIG, 8 placebo); a parent or sibling in just over half the cases (54%); and a grandparent, aunt, or uncle in the remainder. Thirty-five children (59%) reported sore throats before or on admission, but only 13 (37%) of these were receiving antibiotic treatment. In only 4 patients was the antibiotic course prescribed and taken appropriately. Twelve children (20%) had positive throat culture for *Streptococcus pyogenes* on admission. Nine

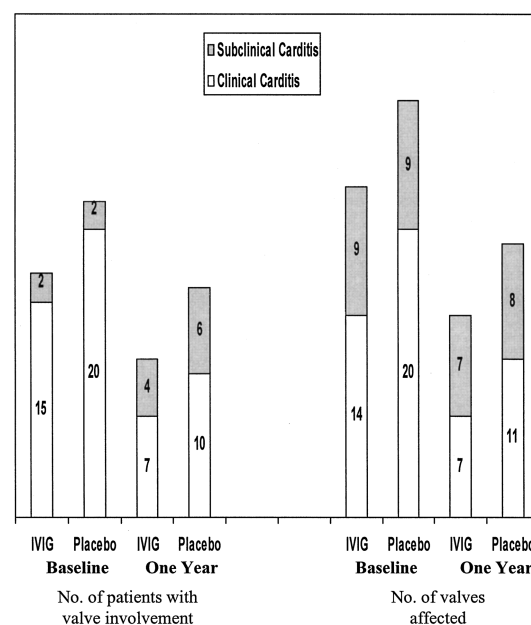


Figure 2. Assessment of valve involvement, clinically and with echocardiography, on enrollment and 1 year later. Left, Number of patients with valve involvement. Right, Number of valves affected.

were M typed; of these, 5 could not be typed, 2 were NZ 1437, 1 was M53, and 1 was M53/80. All 61 had serological confirmation of a preceding streptococcal infection.

There was no difference in the level of ESR, C-reactive protein, or other acute-phase reactants at 6 weeks (Figure 1). A significant difference in ESR between groups was seen at week 2 but did not persist. The time taken for the ESR to drop to ≤ 30 mm/h was similar in both groups.

There were 17 patients with carditis in the IVIG group and 22 in the placebo group at baseline (Table 3 and Figure 2). No significant difference in reduction in carditis when assessed with and without subclinical carditis was seen at 1 year, whether assessed on the basis of affected patients or affected

TABLE 3. Number of Patients and Grades of Severity of Carditis at Timed Intervals

	Baseline		6 weeks		26 weeks		52 weeks	
	IVIG (n=27)	Placebo (n=32)	IVIG (n=27)	Placebo (n=32)	IVIG (n=27)	Placebo (n=30)	IVIG (n=27)	Placebo (n=32)
Mitral regurgitation								
Severe	0	2	0	2	1	1	1	1
Moderate	4	4	4	5	1	5	1	4
Mild	5	6	5	3	5	1	1	2
Subclinical	5	6	6	5	2	4	5	6
Nil	13	14	12	17	18	19	19	19
Aortic regurgitation								
Severe	0	0	0	0	0	0	0	0
Moderate	2	5	2	3	1	2	1	2
Mild	3	3	1	1	2	1	3	2
Subclinical	4	3	3	3	3	3	2	2
Nil	18	21	21	25	21	24	21	26

TABLE 4. Patients and Affected Mitral and Aortic Valves Showing Return to Normal Between Enrollment and 1-Year Follow-Up

	Patients Losing Clinical Signs of Carditis, %		Valves Losing Evidence of Carditis, %	
	IVIG	Placebo	IVIG	Placebo
Clinical assessment only	53	50	50	45
Clinical and echocardiographic assessment	35	27	39	35

Echocardiography adds a small number of patients with a diagnosis of carditis (Figure 2) and records fewer patients who have lost their valve involvement at 1 year.

valves (Figure 2 and Table 4).^{16,17,21} Preliminary stratification had resulted in an equal proportion of patients with nil, mild, or severe carditis in the treated and placebo groups, but some imbalance occurred because of withdrawals. There was no difference in the relative proportion of patients exhibiting mild, moderate, or severe carditis over time assessed at 2, 4, or 6 weeks and at the 6-month and 1-year follow-up visits (Table 3). There were no differences in indexes of left ventricular function between the IVIG and placebo groups at baseline and at follow-up. Shortening fraction was normal at all time points (Figure 3).

Aspirin was used for relief of symptomatic arthritis only; 75% in the control group and 55% in the IVIG group were treated until resolution of symptoms. Analysis of these patients with and without carditis showed no influence of aspirin on cardiac outcome.

Discussion

This is the first reported use of IVIG in ARF. IVIG has now been proven to be efficacious for Kawasaki disease, idiopathic thrombocytopenic purpura, and polymyositis-dermatomyositis.^{7,8,22} The benefits seen in Kawasaki disease are particularly relevant to ARF, because the incidence of coronary artery aneurysms is significantly reduced by IVIG administration. A large variety of immunological mechanisms may be involved in the pathogenesis of ARF, including

cross-reactive antibodies, release of cytokines, activation of T and B cells, and immune complex formation.^{6,23} IVIG may modulate the expression of cytokines and suppress activated cytotoxic T cells.

Given the activation of inflammatory mediators, it was hoped that IVIG would minimize the valvulitis in ARF, but our study did not show this. Possible explanations for a lack of demonstrable efficacy of IVIG in this study include the pathogenesis of ARF, the dose and type of IVIG preparation used, and the power of the study. The effectiveness of IVIG in Kawasaki disease is dependent on the patient receiving IVIG within 10 days of the onset of symptoms.²⁴ In ARF, there is characteristically a 1- to 3-week interval from the initiating group A streptococcal throat infection and the onset of symptoms. A further delay in diagnosis may occur as the Jones criteria for ARF become fulfilled over time, both before and after medical attention is received. In this study, the average duration of symptoms before the first infusion was 9 days, a reflection of the combined time to seek medical care and time for diagnosis to be made. This delay may have allowed the inflammatory process to advance, potentially negating any benefit of IVIG. The study was carried out in an urban setting, and a significant improvement in the time from onset to diagnosis is unlikely to be achieved. The dose of IVIG given to these patients was probably adequate, because the initial dose was similar to that used in Kawasaki disease.²⁴ This initial dose was given over 2 days, a protocol designed to minimize the effects of volume loading on patients in incipient heart failure. The protocol also included further maintenance doses 2 and 4 weeks later to allow for the protracted course of ARF. A number of different preparations of IVIG have been used in the studies of Kawasaki disease and idiopathic thrombocytopenic purpura with similar efficacy.⁹ Although no studies have compared different preparations, it is likely that most IVIG products are therapeutically equivalent.²⁵ It is unlikely that the lack of effect of IVIG was a result of the preparation used. There may have been advantages in using a preparation made from New Zealand plasma, which should contain antibodies against local streptococcal strains.

No medical intervention has been shown to limit the degree of valve damage produced by ARF. Aspirin relieves symptoms but does not influence outcome. In 1954, Illingworth et al²⁶ reviewed 170 articles and found no influence of aspirin on carditis, confirmed again by the UK-US joint report.²⁷ The meta-analysis on corticosteroid treatment by Albert et al²⁸ showed minor variation in outcome of smaller studies but no evidence of limitation of valve lesions, although a response of $\leq 10\%$ could have been missed. Despite these studies, many patients worldwide with ARF continue to receive salicylates and steroids.

The present study was designed to detect an improvement in the natural history of carditis by IVIG if there had been a 60% improvement in the treated group and a 25% improvement in control subjects at 1 year. Such a benefit was predicted if IVIG proved as effective as it is in Kawasaki disease. In the largest study of this condition, coronary aneurysms were detected in 14 of 79 patients (18%) treated with aspirin compared with 3 of 79 (4%) treated with aspirin

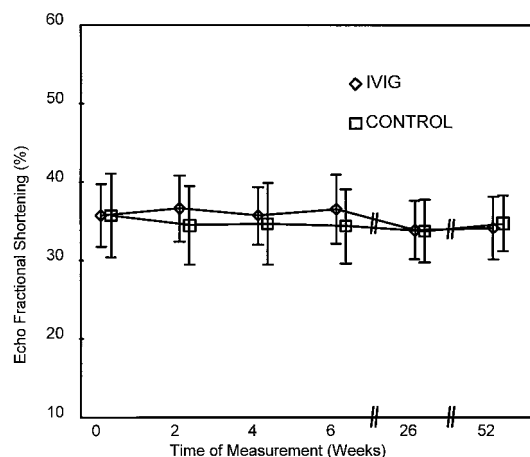


Figure 3. Echocardiographic shortening fraction values are normal at all time points in both groups.

plus IVIG.²¹ Other studies report a similar response.⁹ If IVIG had a similar effect on rheumatic fever, our study would have shown a highly significant benefit ($P > 0.001$). If IVIG has an influence on rheumatic fever, it is clearly not of this order.

In the older literature, murmurs disappeared in 40% of 250 cases,²⁹ 23% of 243 cases,³⁰ and 32% of 216 cases over 1 to 2.5 years.³¹ Reports in smaller studies are congruent with these figures, and a recent study reported the disappearance of murmurs in 45 of 123 patients (37%).³² It is notable that when follow-up echocardiographic studies were undertaken, 100% of subjects who originally had moderate or severe and 50% of those who had mild mitral regurgitation still showed regurgitation at follow-up.³² If, as is likely, the same phenomenon applies to those without echocardiography, the revised rate of disappearance of carditis is 37%. In our study, using echocardiographic assessment, 27% of patients given placebo showed a return to normal, an indication of the natural improvement of valvulitis in ARF. Similarly, 35% of valves with mitral or aortic regurgitation returned to normal (Table 4).

Our study provides convincing evidence that IVIG is not as efficacious in rheumatic fever as in Kawasaki disease. It happens, though, that there is a 4% to 5% advantage with IVIG in the reduction of valve lesions both on clinical assessment and on echocardiography (Table 4). If this difference is real, it is predicted that a minimum of 747 subjects (1494 valves) would be required in an expanded randomized controlled trial to demonstrate an advantage with $P = 0.05$ and a power of 90% or 1398 patients (2796 valves) with $P = 0.01$ and a power of 90% with echocardiographic assessment. The equivalent numbers with clinical assessment only are 802 subjects (1604 valves) for $P = 0.05$ and a power of 90% and 1503 subjects (3006 valves) for $P = 0.01$ and a power of 90%.³³ Such a study would be a formidable undertaking.

Although there was no beneficial effect at 1 year of IVIG in this study, it is possible that a late beneficial effect on the incidence of chronic rheumatic heart disease will be found. However, this is unlikely given the natural history of improvement of ARF with time, the initial lack of beneficial effect of IVIG, and the number of patients in the study.

We believe that this study supports the value of echocardiography in assessing ARF and subsequent progress and that it should be regarded as an essential tool in assessing valve damage and its subsequent progress. An echocardiographic assessment of mild aortic or mitral regurgitation provides evidence of carditis with a very low false-positive rate. A false-positive rate occurs also with clinical assessment. Figure 2 shows that valve regurgitation based on echocardiography assessment alone makes only a small contribution to the number of patients diagnosed but confirms that valvular involvement persists quite frequently when physical signs have returned to normal. We continue to fully utilize echocardiography in patient management. The fact that less severely damaged valves have a greater propensity to recover has been established for decades. Judgments about duration of prophylaxis and protection against endocarditis can be made on clinical grounds and will become more secure as experience with the natural history of echocardiography-only valve leaks accumulates.

We showed no benefit from the use of IVIG in ARF. There was no significant reduction in the extent of severity of carditis assessed clinically or by echocardiography. Similarly, there was no improvement in the rate of normalization of other acute inflammatory markers in the patients who received IVIG. From the figures, a very large study would be required to test this definitively with a robust statistical conclusion. This would require an international collaborative study with a uniformly high level of skills and compliance.

Acknowledgments

This work was supported by grant No. 704 from the National Heart Foundation of New Zealand. Dr Voss was a fellow of the National Child Health Foundation, and Dr Wilson was a senior fellow of the National Heart Foundation of New Zealand. We would like to acknowledge the assistance and support of all the nurses, rheumatic fever community workers, echocardiography technicians of Auckland and Green Lane hospitals and the pediatricians of Starship and Middlemore hospitals, especially Dr Ross Nicholson, who provided invaluable help in recruitment and follow-up of patients. We also wish to thank Dr Diana Martin of the Institute of Environmental Science and Research, Wellington, who serotyped the streptococcal isolates.

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Circulation. 2001;103:401-406

doi: 10.1161/01.CIR.103.3.401

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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