Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease

- Australia/New Zealand Heart Failure Research Collaborative Group
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**Abstract**

Background In patients with heart failure, β-blocker therapy improves left-ventricular function after 3-6 months of treatment, but effects of such treatment on symptoms and exercise performance are inconsistent, and the longer-term effects on death and other serious clinical events remain uncertain. We have investigated these issues in a doubleblind, placebo-controlled, randomised trial of the β-adrenergic blocker carvedilol (which also has α-blocking properties). Methods 415 patients with chronic stable heart failure were randomly assigned treatment with carvedilol (207) or matching placebo (208). At baseline, 6 months, and 12 months, we measured left-ventricular ejection fraction, leftventricular dimensions, treadmill exercise duration, 6 min walk distance, New York Heart Association (NYHA) class, and specific activity scale (SAS) score. Double-blind followup continued for an average of 19 months, during which all deaths, hospital admissions, and episodes of worsening heart failure were documented. Findings After 12 months, left-ventricular ejection fraction had increased by 5.3% (2p

**Keywords**

failure, due, randomised, placebo, controlled, trial, carvedilol, patients, congestive, ischaemic, heart, disease

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Summary

Background In patients with heart failure, β-blocker therapy improves left-ventricular function after 3–6 months of treatment, but effects of such treatment on symptoms and exercise performance are inconsistent, and the longer-term effects on death and other serious clinical events remain uncertain. We have investigated these issues in a double-blind, placebo-controlled, randomised trial of the β-adrenergic blocker carvedilol (which also has α₁-blocking properties).

Methods 415 patients with chronic stable heart failure were randomly assigned treatment with carvedilol (207) or matching placebo (208). At baseline, 6 months, and 12 months, we measured left-ventricular ejection fraction, left-ventricular dimensions, treadmill exercise duration, 6 min walk distance, New York Heart Association (NYHA) class, and specific activity scale (SAS) score. Double-blind follow-up continued for an average of 19 months, during which all deaths, hospital admissions, and episodes of worsening heart failure were documented.

Findings After 12 months, left-ventricular ejection fraction had increased by 5-3% (2p=0.0001) and end-diastolic and end-systolic dimensions had decreased by 1.7 mm (2p=0.06) and 3.2 mm (2p=0.001), respectively, in the carvedilol group compared with the placebo group. During the same period that were no clear changes in treadmill exercise duration, 6 min walk distance, NYHA class, or SAS score. After 19 months, the frequency of episodes of worsening heart failure was similar in the carvedilol and placebo groups (82 vs 75; relative risk 1.12 [95% CI 0.82–1.53]) but the rate of death or hospital admission was lower in the carvedilol group than in the placebo group (104 vs 131; relative risk 0.74 [0.57–0.95]).

Interpretation The beneficial effects of carvedilol on left-ventricular function and size were maintained for at least a year after the start of treatment, but carvedilol had no effect on exercise performance, symptoms, or episodes of worsening heart failure. There was an overall reduction in events resulting in death or hospital admission, and a year of treatment with carvedilol resulted in the avoidance of one such serious event among every 12–13 (SE 5) of these patients with chronic stable heart failure.

Lancet 1997; 349: 375–80

Introduction

Despite advances in the treatment of congestive heart failure, the outlook for many patients with this disorder remains poor. In patients with mild or moderate symptoms who receive standard treatment including an inhibitor of angiotensin-converting enzyme (ACE), the annual rate of hospital admission is about 15–20% and the mortality rate about 10%. Treatment with β-blockers may have the potential to reduce morbidity and mortality in heart failure, but there is no unequivocal evidence as yet. However, 3–6 months of treatment with a β-blocker has been clearly shown to increase left-ventricular ejection fraction by about 5% (absolute units) in patients with heart failure of idiopathic or ischaemic aetiology. Such therapy has not produced any consistent effects on symptoms or exercise performance, and whether longer-term treatment will produce clearer benefits for these outcomes or for serious morbidity and mortality remains unclear.

We report here the final results from the Australia/New Zealand Heart Failure Research Collaborative Group trial of carvedilol in 415 patients with heart failure due to ischaemic heart disease. Carvedilol is a β-blocker with α₁-blocking vasodilator properties and with several other potentially advantageous effects, including antioxidant and anti-ischaemic properties. A planned interim analysis from this study after 6 months of follow-up showed an absolute increase of 3.2% in left-ventricular ejection fraction, a reduction in left-ventricular dimensions, no change in exercise performance, and a trend to worsening of symptoms of heart failure among patients assigned carvedilol. We now provide data on the same outcomes after 12 months of follow-up, as well as the risks of death, hospital admission, or worsening heart failure during an average of 19 months of follow-up.

Methods

Patients

Participants were recruited to the trial from 20 hospitals in Australia and New Zealand. Potentially eligible patients had chronic stable heart failure due to ischaemic heart disease (defined as a documented history of myocardial infarction, typical angina, an exercise electrocardiogram positive for ischaemia, or angiographic evidence of coronary disease) and a left-ventricular ejection fraction by radionuclide ventriculography of less than 45%, and were of current New York Heart Association (NYHA) functional class II or III or previous NYHA class II–IV.

Exclusion criteria included current NYHA class IV, heart rate below 50 bpm; sick sinus syndrome; second-degree or third-degree heart block; blood pressure below 90 mm Hg systolic or above 160/100 mm Hg; treadmill exercise duration less than 2 min or more than 18 min (modified Naughton protocol); coronary event or procedure (myocardial infarction, unstable angina, coronary-artery bypass surgery, or coronary angioplasty) within the previous 4 weeks; primary myocardial or valvular disease; current treatment with a β-blocker, β-agonist, or verapamil; insulin-dependent diabetes mellitus; chronic

*Members listed at end of paper

Correspondence to: ANZ Heart Failure Trials Office, Clinical Trials Research Unit, Department of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand
obstructive airways disease; hepatic disease (serum aminotransferase above three times normal); renal impairment (serum creatinine >250 μmol/L); or any other life-threatening non-cardiac disease.

**Design and study treatment**

Before randomisation, 442 potentially eligible patients began 2 to 3 weeks of open treatment with carvedilol. After a test dose of 3·125 mg, treatment began with 3·125 mg twice daily for 1 to 2 weeks, progressing to 6·25 mg twice daily for a further week, if tolerated. The purpose of this open phase was to identify patients who could not tolerate a low dose of carvedilol or who were unlikely to comply with treatment or follow-up requirements. 27% patients were withdrawn from the study during this phase; the reasons for withdrawal have been reported previously.3 The 415 compliant patients who tolerated carvedilol 6·25 mg twice daily were then randomly assigned, under double-blind conditions, continued treatment with carvedilol or matching placebo. Randomised allocation was obtained by telephone call to the Clinical Trials Research Unit randomisation service in Auckland. Treatment assignment was provided by computer, with stratification for clinical centre and a minimisation algorithm to ensure balance for baseline characteristics, treadmill exercise duration, left-ventricular ejection fraction, and of fatal or non-fatal worsening heart failure were planned in advance. Data on deaths, hospital admissions, and episodes of worsening heart failure were obtained throughout an average of 19 months of follow-up; measurements for study outcomes were made at baseline and at 6 months and 12 months after randomisation.

**Study outcomes**

The primary study outcomes were changes in left-ventricular ejection fraction, assessed by radionuclide ventriculography, and treadmill exercise duration, measured with a modified Naughton protocol with 2 min stages. Secondary study outcomes included changes in left-ventricular dimensions, submaximum exercise performance (6 min walk distance6), and symptoms of heart failure described by NYHA class and the specific activity scale (SAS), and the frequency of death, hospital admission, or worsening heart failure. Left-ventricular dimensions were assessed by two-dimensional guided M-mode echocardiography, and all measurements were made from videotapes (ImageVue, Nova Microsonics, Allendale, NJ, USA) at a central laboratory (University of Auckland) by an observer unaware of treatment group and according to American Society of Echocardiography standards.4 An episode of worsening heart failure was defined as any clinically significant deterioration in the patient's condition (for example, an increase in non-study treatment requirements, an increase in NYHA functional class, hospital admission for worsening symptoms of heart failure, or a non-sudden death from worsening heart failure). We collected data on the reasons for and duration of all episodes of hospital admission and on the causes and circumstances of deaths among trial participants. Separate analyses of the combined outcome of death or hospital admission and of fatal or non-fatal worsening heart failure were planned a priori. Data on deaths, hospital admissions, and episodes of worsening heart failure were obtained throughout an average of 19 months of follow-up; measurements for study outcomes were made at baseline and at 6 months and 12 months after randomisation.

**Statistics**

A sample size of 200–225 patients per group was estimated to provide more than 80% power at statistical significance of 0·05 to detect: an absolute change in left-ventricular ejection fraction of 2% or more between the groups (with the assumption of a standard deviation of change in ejection fraction of about 6%); and a change in treadmill exercise duration of 1 min or more between groups (with the assumption of a standard deviation of change in treadmill exercise duration of about 3 min). With a 25–30% annual rate of death or hospital admission,1 such a sample size would also provide reasonable power during 18 months of follow-up to detect any moderate-to-large reduction (eg, a third or more) in this combined endpoint; however, it would probably be inadequate for the detection of all but an extremely large effect of treatment on death alone.

Principal outcome analyses were by intention to treat. Differences between groups from baseline to 12 months in left-ventricular ejection fraction, treadmill exercise duration, left-ventricular dimensions, 6 min walk distance, blood pressure, and heart rate were assessed by two-sample t tests. Each of the symptom scales was analysed by χ². Differences between groups in...
the frequency of death or hospital admission and of episodes of worsening heart failure were analysed with a Cox proportional hazards model. Probability values for two-tailed tests of significance (2p) are given throughout, rounded to one significant figure, except for values greater than 0·1 or less than 0·0001.

Results

The mean age of the participants at entry to the study was 67 years, and 80% were men. 70% were classified as being NYHA functional class II or III at the time of randomisation, and 43% had previously been class IV (table 1). Almost 90% had a history of myocardial infarction, and 42% had had a previous hospital admission for heart failure. 95% were currently receiving drug treatment for the management of heart failure, and 85% were receiving ACE-inhibitor therapy. The average left-ventricular ejection fraction at entry was 29% (SD 8) and the average left-ventricular end-diastolic and end-systolic dimensions were 69 mm (10) and 57 mm (11). The average treadmill duration was 10·5 min (4), and the average 6 min walk distance 392 m (74). Treadmill exercise duration was limited by myocardial ischaemia (angina or ST-T changes) in 24% of patients.

Figure 1 shows the flow of patients through the trial. Complete data on mortality were available for all 415 patients throughout follow-up. Other data were available for 392 patients at 6 months (97% of survivors), 373 at 12 months (96% of survivors), and 353 (95% of survivors) at the scheduled end of follow-up (between Aug 6, 1994, and June 21, 1995; mean 19 months). 361 patients completed 6 months of study treatment (90% of survivors), 329 completed 12 months of treatment (85% of survivors), and 298 (80% of survivors) were still on study treatment at the scheduled end of follow-up. After 6 months, there was a small excess of withdrawals from treatment in the carvedilol group (30/71; 2p=0·01), but by the end of follow-up the numbers of withdrawals from the two groups were similar (41 vs 30; 2p>0·1).

Among the 298 patients still taking study treatment at the end of follow-up, the mean dose was similar in the carvedilol and placebo groups (41 mg vs equivalent of 45 mg daily, 2p>0·1). By the scheduled end of follow-up, 30% of patients assigned treatment with carvedilol had died or were no longer receiving study treatment, 7% were taking 12·5 mg daily, 16% 25 mg daily, and 48% 50 mg daily. Among those receiving other therapy for heart failure, there was no significant change in the mean dose of furosemide, captopril, or enalapril from baseline to the scheduled end of follow-up.

From baseline to 12 months, supine and maximum exercise heart rates fell by 6·8 bpm and 20·2 bpm, respectively (both 2p<0·0001), in the carvedilol group compared with the placebo group. Supine and maximum exercise blood pressures declined by 5·2/3·7 mm Hg (2p=0·008/0·006) and 10·8/3·0 mm Hg (2p<0·0001/0·07) respectively, in the carvedilol group compared with the placebo group during the same period. The fall in maximum exercise-rate/pressure product from baseline to 12 months was 4201 mm Hg bpm (22%; 2p<0·0001). Between the 6-month and 12-month visits, there was no evidence of any attenuation of the differences between the groups in heart rate or blood pressure (all 2p>0·1).

Left-ventricular ejection fraction increased from 28·4% at baseline to 33·5% at 12 months among patients assigned carvedilol (figure 2). The placebo group showed little change; therefore, there was a difference between the groups at 12 months of 5·3% (95% CI 2·9 to 7·7). Left-ventricular end-diastolic and end-systolic dimensions were 1·7 mm (2p=0·006) and 3·2 mm (2p=0·001) smaller in the carvedilol group than in the placebo group after 12 months (figure 2). Between 6 and 12 months, there was no clear evidence of any attenuation of the differences between the groups in ejection fraction or left-ventricular dimensions (all 2p>0·1).

There was no significant difference between the carvedilol and placebo groups in treadmill exercise duration at 12 months (mean difference 7 s [95% CI 0·5 to 1·3], 2p=0·15).
378 Vo1349 average of 19 months of follow-up since each patient can contribute only one hospital admission to a single analysis, but All admissions Ail cardiovascular disease

Table 3: Causes of death and hospital admission during an average of 19 months of follow-up

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Carvedilol (n=208)</th>
<th>Placebo (n=207)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>23</td>
<td>15</td>
<td>0.92 (0.45-1.91)</td>
</tr>
<tr>
<td>Sudden*</td>
<td>30</td>
<td>31</td>
<td>0.90 (0.38-2.11)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4</td>
<td>4</td>
<td>0.99 (0.25-3.96)</td>
</tr>
<tr>
<td>All cardiovascular deaths</td>
<td>18</td>
<td>20</td>
<td>0.89 (0.47-1.68)</td>
</tr>
<tr>
<td>Non-cardiovascular deaths</td>
<td>2</td>
<td>6</td>
<td>0.32 (0.07-1.60)</td>
</tr>
<tr>
<td>All deaths</td>
<td>20</td>
<td>26</td>
<td>0.78 (0.42-1.46)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause of hospital admission:</th>
<th>Carvedilol (n=151)</th>
<th>Placebo (n=146)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>23</td>
<td>33</td>
<td>0.68 (0.40-1.07)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>25</td>
<td>34</td>
<td>0.70 (0.42-1.18)</td>
</tr>
<tr>
<td>Other cardiovascular disease</td>
<td>40</td>
<td>38</td>
<td>1.07 (0.68-1.66)</td>
</tr>
<tr>
<td>All cardiovascular disease</td>
<td>70</td>
<td>83</td>
<td>0.82 (0.59-1.12)</td>
</tr>
<tr>
<td>Non-cardiovascular disease</td>
<td>51</td>
<td>69</td>
<td>0.70 (0.49-1.01)</td>
</tr>
<tr>
<td>All admissions</td>
<td>99</td>
<td>120</td>
<td>0.77 (0.59-1.00)</td>
</tr>
</tbody>
</table>

*Within 24 h of onset of new symptoms or death of a previously symptom-free patient.
†Subtotals and total do not equal sum of individual causes of hospital admissions since each patient can contribute only one hospital admission to a single analysis, but patients with several hospital admissions for different causes may contribute to more than one analysis.

Discussion

We have found that in patients with chronic stable heart failure due to ischaemic heart disease, the effects of carvedilol on left-ventricular function were maintained for at least a year from the start of treatment, with no apparent loss of the initial short-term improvement. These effects were achieved against a background of standard drug therapy for heart failure, including ACE inhibitors for more than 80% of patients. The increase in left-ventricular ejection fraction and the decrease in left-ventricular dimensions suggest a sustained improvement in intrinsic myocardial function. Treatment with carvedilol did not, however, confer any changes in maximum or submaximum exercise performance or in the severity of symptoms assessed by NYHA class or SAS score. The absence of any functional or symptomatic improvement after 12 months is consistent with the absence of any clear difference in the overall frequency of worsening heart failure during 19 months of treatment and follow-up. Thus, there was an apparent dissociation of changes in left-ventricular function
from changes in exercise capacity and symptoms of heart failure. Whether there are benefits of β-blocker therapy for these outcomes in other subgroups of patients with heart failure remains uncertain. There have been reports of such benefits in some, though not all, trials of β-blockers in patients with idiopathic cardiomyopathy and in other trials among patients with more severe heart failure. Further randomised studies among such patients would help to show more clearly whether there are subgroups of patients whose symptoms could benefit from treatment with β-blockers.

In addition to improving left-ventricular function, treatment with carvedilol was also associated with a lower overall risk of serious clinical events resulting in death or hospital admission. During the follow-up period, such events occurred in 63% of the placebo group and in 50% of the carvedilol group. This difference represents the avoidance each year of one serious event among every 12-13 patients treated with carvedilol (with 95% CI confidence limits ranging from the avoidance of one event in every seven patients to the avoidance of one event in every 60 patients). This improvement did not seem to be associated with one particular type of event—there were similar trends for deaths and hospital admissions, and for all serious cardiovascular events, ischaemic-heart-disease events, heart-failure-related events, and non-cardiovascular events. The degree to which the benefits of carvedilol are a consequence of β-blockade per se or of the other potentially beneficial properties of this agent remains uncertain. The overall treatment effect on death or hospital admission (ie, a reduction in risk of 26%) is, however, consistent with the results of several other trials of β-blockers in patients with heart failure, mostly of idiopathic aetiology as well as results from the limited subgroups of patients with heart failure in the trials of β-blockers in patients with myocardial infarction.

A combined analysis of four trials in the USA of patients with heart failure also found a reduction in deaths and hospital admissions after treatment with carvedilol. The reduction in risk of hospital admission in those studies was similar to that in our study, but the reduction in mortality in the US trials (relative risk 0.59 [95% CI 0.45-0.77]) after 6.5 months appeared to be larger than ours (relative risk 0.76 [0.42-1.36]). However, the number of deaths in each of the four US trials of carvedilol was small, and the combined total of only 53 deaths was similar to the total number in our study. The apparent difference between the US studies and our study in the effects of carvedilol on survival was not statistically significant (2p for heterogeneity >0.1) and could therefore have occurred by chance rather than as a consequence of any particular difference in selection of patients or study design.

Trials of carvedilol so far have recorded too few deaths, even in combination, for reliable calculation of the size of the effect of this drug on survival in patients with heart failure. However, if a reduction in mortality of 25% or more (as suggested by these studies) were confirmed in larger-scale, longer-term trials of carvedilol, there would be important implications for the management of patients with heart failure. Even among patients with mild symptoms, one death would be avoided each year among every few dozen patients treated. Given this possible benefit and the findings, from this and other trials, that the drug is well tolerated when introduced at low doses, carvedilol has the potential to become part of standard therapy for many patients with heart failure. However, the present clinical trial experience with carvedilol is too limited for this treatment to be widely recommended for the management of patients with heart failure. Only 1658 patients have been studied for an average of 10 months in eight randomised trials of this drug. These studies were principally designed to investigate the effects of carvedilol on left-ventricular function and exercise performance. Trials of appropriately larger size (ie, several thousand patients) and duration (ie, several years), designed to investigate the effects of carvedilol on survival are now required to show whether this drug can be recommended as first-line therapy for heart failure, together with ACE inhibitors.

Australia/New Zealand Heart Failure Research Collaborative Group

Writing Committee S MacMahon, N Sharpe, R Doughty.

Participating centres (study investigator)—Australia: Austin Hospital, Melbourne (H Krum, A Tonkin, J Trotter); Fremantle Hospital, Fremantle (R Burton, J Garrett, G Lane); Illawarra Regional Hospital, Wollongong (D Owensby, J Ryan); Launceston Hospital, Tasmania (J Shepherd, B Singh); Preston and Northcote Community Hospital, Melbourne (B Jackson*, G Rudge); Princess Alexandra Hospital, Brisbane (J Stephensen, S Woodhouse); Prince Henry Hospital, Sydney (P Davidson, J Turner, W Walsh*); Repatriation Hospital, Melbourne (J Bradbury, A Hamer*); Royal Brisbane Hospital, Brisbane (D Cross*, C Hall); Royal Hobart Hospital, Hobart (V Kimber, C Spoulding, A Thompson*); Sir Charles Gardiner Hospital, Perth (M Cross, PL Thompson*); Queen Elizabeth Hospital, Adelaide (J Horowitz*, S Leslie, Y Zhang); Wesley Hospital, Brisbane (D Colquhoun*, B Hicks); Woden Valley Hospital, ACT (T Jeffery*, P Tavernier).

New Zealand: Auckland Hospital, Auckland (C Bond, R Dougherty*, J Murphy, N Sharpe*); Christchurch Hospital, Christchurch (C Hall, H Ikram*, M Richards*); Dunedin Hospital, Dunedin (C Low*, D Scott); Napier Hospital, Napier (G Brown, G Lewis*); Tauranga Hospital, Tauranga (J Bruning, L Naint*); Waikato Hospital, Hamilton (A Clayton, J Crawford, H McAleer*).

Coordinating centre (study co-primary investigators): Clinical Trials Research Unit of the University of Auckland is supported by a programme grant from the Health Research Council of New Zealand. We thank Kathy Bos for assistance in the production of the data-collection forms used in this study.

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References

Familial intracranial aneurysms

Antti Ronkainen, Juha Hernesniemi, Matti Puranen, Lea Niemitukia, Ritva Vanninen, Markku Ryynänen, Helena Kuivaniemi, Gerard Tromp

Summary

Background We set out to determine the prevalence of incidental intracranial aneurysms in first-degree relatives aged 30 years or more of people with intracranial aneurysms, and to see if polycystic kidney disease contributes to the aggregation of familial intracranial aneurysms.

Methods 91 families with two or more affected members had previously been identified from a 14 year series of 1150 intracranial aneurysm patients treated at the University Hospital of Kuopio, Finland. Magnetic resonance angiography was used as a preliminary screening method, followed by conventional four-vessel angiography to verify suspected aneurysms. Participants were also screened for polycystic kidneys by ultrasonography.

Findings Incidental aneurysms were detected in 40 individuals: 38 of 438 individuals from 85 families without polycystic kidney disease or other diagnosed heritable disorders, and two of 22 individuals from six families known to have polycystic kidney disease. The crude and age-adjusted prevalence of incidental intracranial aneurysms among screened first-degree relatives was 8.7 (SE 1.3)% (95% CI 6.2-11.7) and 9.1 (1.4)% (6.2-11.7), respectively, for the familial group and the crude prevalence for the polycystic kidney group was 9.1 (6.1)% (1.1-29.2).

Interpretation Our results demonstrate a high prevalence of incidental intracranial aneurysms among first-degree relatives aged 30 years or older of patients with the condition and indicate that the risk of having an aneurysm is about four times higher for a close relative than for someone from the general population. Also, polycystic kidney disease families are a small fraction of the familial intracranial aneurysm families.

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Departments of Neurosurgery (A Ronkainen MD, J Hernesniemi MD), Clinical Radiology (M Puranen MD, L Niemitukia MD, R Vanninen MD), and Obstetrics and Gynaecology (M Ryynänen MD), University Hospital of Kuopio, PL 1777, 70210 Kuopio, Finland; and Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI, USA (G Tromp PhD, H Kuivaniemi MD),

Correspondence to: Dr Antti Ronkainen

Introduction

About one-quarter of cerebrovascular deaths are due to subarachnoid haemorrhage (SAH). SAH is a devastating disease, since about half the patients die due to primary bleeding or to subsequent complications, and many of the survivors will need extended rehabilitation to continue an independent life. This poor outcome has changed little during the past two or three decades, even though the treatment of SAH has become a daily routine in neurosurgical centres. The economic impact of SAH is severe because it most often affects patients in their 40s and 50s during their most productive years. As many as 80-90% of SAHs are caused by ruptured intracranial aneurysms (IAs). Up to 60% of individuals who experience aneurysmal SAH will die before hospital admission. After hospital admission, about one-third will die, about one-sixth will recover with a severe disability, about one-sixth will have some disability, and about one-third will have excellent outcome. Increasing experience in treating ruptured IAs, either with advanced microsurgical or with endovascular techniques, has resulted in improved outcomes for elective surgery of unruptured IAs. The per case mortality for treatment of unruptured IAs involving elective surgery is below 2%, whereas the per case mortality for treatment of ruptured aneurysms that involves emergency surgery may exceed 30% with mortality due to surgery rarely exceeding 30%. In addition, the techniques of endovascular surgery such as selective occlusion of aneurysms with detachable balloons and metallic coils have the promise of reducing surgical complications and mortality even further. Given the strikingly different outcomes, it is evident that treating IAs before rupture would save lives.

Screening the population at large for the presence of IAs is not feasible, but identification of groups with increased risk may make screening feasible. Familial aggregation of IAs has been observed and IAs are often associated with the autosomal dominant form of polycystic kidney disease (PKCD). 6-20% of IA cases may be familial with two or more confirmed IA cases in the same family in the absence of any signs of other hereditary disorders. Younger age of onset, presence of IAs among twins, and the fact that in siblings the age of onset is closer than expected by chance support the hypothesis that familial intracranial aneurysms (FIA), in the absence of other predisposing heritable disorders, are a distinct disease entity. The risk of at least two individuals in a family being