Thoracic Aortic Surgery

Epidemiology, Outcomes, and Prevention of Cerebral Complications

CHRISTIAN OLSSON
Dissertation presented at Uppsala University to be publicly examined in Robergsalen, Akademiska sjukhuset, Ingång 40, Uppsala, Wednesday, May 31, 2006 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

The mortality of thoracic aortic diseases (mainly aneurysms and dissections) is high, even with surgical treatment. Epidemiology and long-term outcomes are incompletely investigated. Stroke is a major complication contributing to mortality, morbidity, and possibly to reduced quality of life.

Study I Increasing incidence of thoracic aortic diseases 1987 – 2002 was demonstrated (n=14229). Annual number of operations increased eight-fold. Overall long-time survival was 92%, 77%, and 57% at 1, 5, and 10 years. Risk of operative and long-term mortality was reduced across time.

Study II 2634 patients operated on the proximal thoracic aorta (Swedish Heart Surgery register) were examined. Aortic valve replacement, coronary revascularization, emergency operation, and age were independently associated with surgical death. Long-term mortality was similar for aneurysms and dissections. Operative mortality was reduced (13.7% vs 7.2%) for aneurysms but remained unchanged (22.3% vs 22.4%) for dissections across time.

Study III 65 patients underwent selective antegrade cerebral perfusion (SACP) uni- or bilaterally. Stroke was significantly more common after unilateral SACP (29% vs 8%, p=0.045), confirmed by propensity score-matched analysis. Subclavian artery cannulation with Seldinger-technique entailed vascular complication in one case (1.5%).

Study IV Near-infrared spectroscopy (NIRS) was used to monitor cerebral tissue saturation (rSO2) during SACP in 46 patients. Lower rSO2 were encountered (1) in patients suffering a stroke (2) with unilateral SACP, and (3) in the affected hemisphere of stroke victims. A decrease of rSO2 by 14 – 21% from baseline increased the risk of stroke significantly.

Study V Quality of life (QoL) in 76 survivors of thoracic aortic surgery was examined with the SF-36 health questionnaire. Except for pain, QoL was reduced in all dimensions. QoL was not affected by acuity of operation. Tendencies of lower QoL after descending aortic operations, after major complications, and with persistent dysfunction were non-significant.

Keywords: Aorta, Thoracic, Aortic aneurysms, Aortic disease, Cardiovascular surgical procedures, Epidemiology, Registries, Treatment outcome, Survival analysis, Cerebral infarction, Near-infrared spectroscopy, Quality of life, Perfusion

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List of papers

The thesis is based on the following papers, referred to in the text by their roman numerals.


II Olsson C, Eriksson N, Ståhle E, Thelin S. Surgical and long-term mortality in 2634 consecutive patients operated on the proximal thoracic aorta. Submitted


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<tr>
<td>AUC</td>
<td>Area under curve</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>CDR</td>
<td>Cause of death register</td>
</tr>
<tr>
<td>CL</td>
<td>Confidence limits</td>
</tr>
<tr>
<td>COD</td>
<td>Cause of death</td>
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<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
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<tr>
<td>HCA</td>
<td>Hypothermic circulatory arrest</td>
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<tr>
<td>HDR</td>
<td>Hospital discharge register</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ICD</td>
<td>International classification of diseases</td>
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<td>IRAD</td>
<td>International registry of aortic dissection</td>
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<td>NCSP</td>
<td>Nomesco classification of surgical procedures</td>
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<tr>
<td>NIRS</td>
<td>Near-infrared spectroscopy</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
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<tr>
<td>RR</td>
<td>Risk ratio; Relative risk</td>
</tr>
<tr>
<td>rSO2</td>
<td>Regional oxygen saturation index</td>
</tr>
<tr>
<td>SACP</td>
<td>Selective antegrade cerebral perfusion</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
</tr>
<tr>
<td>SjvO2</td>
<td>Jugular venous bulb saturation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form-36 health questionnaire</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardized mortality rate</td>
</tr>
<tr>
<td>TAA</td>
<td>Thoracic aortic aneurysm</td>
</tr>
<tr>
<td>TAAA</td>
<td>Thoracoabdominal aortic aneurysm</td>
</tr>
<tr>
<td>TAD</td>
<td>Thoracic aortic disease</td>
</tr>
<tr>
<td>TCD</td>
<td>Transcranial Doppler</td>
</tr>
<tr>
<td>TND</td>
<td>Temporary neurological dysfunction</td>
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</table>
Surgical diseases of the thoracic aorta are, at least in comparison with other cardiovascular conditions, rare. To an extent they are diseases of the ageing population, associated with its prevalence of eg atherosclerosis and hypertension and often, “vascular surgery is the surgery of ruins” as expressed by Rutherford. Yet, the literature on thoracic aortic surgery is extensive and the subject undoubtedly cherished by cardiac surgeons – why?

First, thoracic aortic diseases are inherently lethal conditions not only amenable to surgery but potentially cured by operation, in terms of prolonged life and restored life expectancy. Second, patients with acute forms of thoracic aortic disease are in fact often younger, otherwise healthy individuals subjected to the worst vascular catastrophe imaginable with an appalling death toll. Third, despite progress of medicine in general and cardiac surgery in particular, the drastic improvement in outcomes is still wanted. For example, perfusion strategies for protection of the brain has come full circle: from selective antegrade perfusion as performed by DeBakey, to hypothermic circulatory arrest, to retrograde cerebral perfusion and back again to antegrade perfusion, reflecting the frustration of surgeons in pursuit of that holy grail providing safer operations, simpler techniques and better results. Finally, thoracic aortic diseases are increasing, requiring more operations, vast amounts of resources, and difficult management decisions to be based on as sound evidence as possible.

The thesis deals with surgical diseases of the thoracic aorta. A spectrum of the conditions – by and large aneurysms and dissections – are examined: epidemiology, surgical and long-term mortality by register studies; cerebral perfusion and monitoring in clinical studies and postoperative quality of life in a follow-up study. Consideration of other end-points than short- and long-term mortality has been underlined repeatedly. In consequence, morbidity, with emphasis on stroke, as well as quality of life after surgery has been studied. With the sought broadening of the perspective, loss of focus and depth inevitably follows. At best, the thesis serves as a source of continued and improved studies in the surgical treatment of thoracic aortic disease.
Introduction

Surgical thoracic aortic disease (TAD) includes many conditions subject to a variety of classifications:

**Pathology**
Aneurysm, pseudoaneurysm, dissection, dilatation, intramural hematoma, ulcer

**Etiology**
Hypertension (essential or secondary to eg coarctation, pregnancy)
Vessel wall abnormality (media degeneration, connective tissue disorder, aortitis)
Genetic predisposition
Congenital abnormality (eg bicuspid aortic valve)
Iatrogenic (acute or late procedure-related)
Trauma

**Anatomy**
Ascending aorta, aortic arch, descending aorta, thoracoabdominal aorta
Aortic dissection:
*Stanford classification*: type A (proximal), type B (distal) [1]
*DeBakey classification*: type I–III b [2]
Thoracoabdominal aneurysm:
*Crawford classification*: type I–IV [3]

**Clinical presentation**
Emergency – acute – elective (chronic)
Rupture – contained rupture/leak – intact
Rupture:
*Periaortic, mediastinal*
*Pericardial* (→ cardiac tamponade)
*Pleural* (→ hemothorax, exsanguination)
Severe symptoms – moderate to mild symptoms – asymptomatic
*Crawford classification* [4]
Diagnostic and procedural codes

International classification of diseases

The International classification of diseases (ICD), maintained by the World Health Organization (WHO) since 1948, classify diseases and health conditions systematically with diagnostic codes. An initial letter define the organ system or alike, and the following three digits code for specific conditions. Normally, the three first positions constitute a mother-code equivalent to a diagnosis, whereas the fourth digit can specify a location or detail a condition. The ninth revision (ICD-9) established internationally in 1975 and in Sweden in 1986, is based on three-digit codes adding a letter in the fourth position. The completely revised and reorganized tenth revision, endorsed by the WHO in 1994, was introduced in Sweden in 1997–1998.

Nomesco Classification of surgical procedures

Nomesco, the Nordic medico-statistical committee, acts a permanent statistical committee under the Nordic Council of ministers since 1979. The first issue of the Nomesco classification of surgical procedures (NCSP) was published in 1996 and came into use in Sweden concurrently with the ICD-10 in 1997. In a five-position code, the first letter codes for organ system, the second and third letters for parts of the organ system and the following two digits for the specific procedure on that part of the organ. Prior to the NCSP, the WHO ICPM (International classification of procedures in medicine), with national modifications, was in use for procedural coding in a four-digit format that eventually was abandoned due to inconsistency and incompleteness.

National health registers

For health-related purposes, there are two main sources of information: the registers maintained by the Swedish Health and Welfare Board and by Statistics Sweden. The former include the hospital discharge register (HDR) and the cause of death register (CDR), the latter the general population census and vital statistics. The CDR is rapidly and continuously updated; the population census is annual. Pivotal for information retrieval from the registers are the twelve-digit personal identification numbers unique for every individual residing in Sweden that allows record linkage between the registers.
The Hospital Discharge Register

The HDR was conceived in 1962. Since 1987, it is nationwide with complete coverage of in-patient events including the patient’s age and sex; the personal identification number; date of admission, procedures and discharge; hospital department and up to eight discharge diagnostic codes and procedural codes each [5]. The validity and reliability of the register have been assessed repeatedly. In a large study (n=900) of unselected patients in internal medicine, gynecology and surgical departments, the main diagnosis was incorrect in 10–17% depending on the number of diagnoses and the strictness of judgment in the validation [6]. In general, coding for well-defined diagnoses was better than for symptom-oriented diagnoses. Of 430 operations, nine (2%) had incorrect coding and 13 codes for major procedures were missing [6].

The Cause of Death Register

Death certificates are issued within 24 hours. Cause of death (COD) forms are completed at the earliest convenience, pending autopsy reports. The CDR certificate includes, apart from information on the subject, information on place, date and time of death. COD is reported as a text-string and by ICD diagnostic code and is multi-level: direct COD, cause of COD, underlying cause, and contributing disease, with approximate duration for each. Hereby, terminal COD such as ventricular fibrillation, apnea, and exsanguination are noted but not registered as COD; rather, the underlying cause(s) are. Misclassifications are uncommon, but COD data are sometimes incomplete, resulting in spurious COD [7]. The frequency of clinical autopsy has been reduced from a high 80% to around 30% during the last decades, increasing the number of incomplete COD data [8].

The Swedish heart surgery register

The Swedish Heart Surgery Register was established in 1992. It contends administrative, demographic and clinical information on every patient undergoing cardiovascular surgery in Sweden. Up to 101 items of information can be retrieved from the designated report card. The coverage is complete; all Swedish departments of cardiovascular surgery report all of their patients to the register. Reporting is continuous and processed data are referred back from the register to the departments for corrections and replacement of missing data before the completion of the register annual report [9]. The contents of the register have been expanded over time, and most recently the EuroSCORE risk score was added to the database.
**Epidemiology**

Population-based studies of TAD with a sufficient number of subjects and events, and adequate follow-up are scarce. As apparent from table 1, the case-mix, study method and reporting of findings also vary. Two studies from the same geographical area report overall population-adjusted incidence figures for TAD and thoracic aortic aneurysm (TAA) to 5.9 and 10.4/100 000 respectively [10, 11]. However, the study of Bickerstaff et al [10] was undertaken before the widespread use of CT and echocardiography for diagnosis of TAD. The incidence of thoracic aortic rupture and/or aortic dissection is in the 3–5/100 000/year interval [12, 13]. In a Swedish autopsy-study including 205 subjects, prevalence of asymptomatic thoracic aortic aneurysm is estimated to 437–489/100 000 [14].

Generally, a slight female preponderance is reported with TAD or TAA (female: male ratio 1.04–1.57) [10, 11, 15] whereas the opposite is reported for aortic dissection (male: female ratio 1.5–2.2) [12, 13, 16]. In all studies, the average age at diagnosis is higher in women (70–77 years) than in men (63–70 years).

**Natural history**

The fate of the patient with non-surgically treated TAD is dismal. Ruptured thoracic aortic aneurysms carry an 97–100% [15, 17] mortality. In acute aortic dissection type A, mortality is over 50% within 24 hours without operation, climbs to 84% within a week and to 90–100% within 3 months [16, 18, 19].

Aortic rupture is the major cause of death in TAD, accounting for 20–77% of deaths [11, 17, 20-22]. Aortic diameter is the major risk factor for rupture, and risk is significantly increased (approaching 50%, or 5-fold that of smaller aortic diameters) when it exceeds 6.0 cm in the ascending aorta or 7.0 cm in the descending aorta [20, 22-25]. Accordingly, indication for elective surgery at 5.5 and 6.5 cm aortic diameter (ascending and descending segments, respectively) is suggested, to avoid reaching a “hinge-point” where rupture risk increases steeply [23-25].

From a prospective register-study including 1600 patients it is calculated that the annual risk of rupture, dissection, or death is 14.1% when the ascending aortic diameter is 6.0 cm, thus far exceeding the risk of elective operation [24]. With conservative management of TAD, average time to aortic rupture is 2–4 years [10, 11, 22].
Table 1. Incidence and natural history of thoracic aortic disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>Study pop</th>
<th>n</th>
<th>Case-mix</th>
<th>Overall</th>
<th>30-day</th>
<th>1-year</th>
<th>5-year</th>
<th>10-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bickerstaff</td>
<td>1951-1980</td>
<td>45,000</td>
<td>72</td>
<td>TAA, TAAA, AD</td>
<td>6.1</td>
<td>5.5</td>
<td>5.9</td>
<td>n/a</td>
<td>39</td>
</tr>
<tr>
<td>Johansson</td>
<td>1980, 1989</td>
<td>1,500,000</td>
<td>158</td>
<td>Rupt. TAA, AD</td>
<td>n/a</td>
<td>n/a</td>
<td>5</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Clouse</td>
<td>1980-1994</td>
<td>100,000</td>
<td>133</td>
<td>TAA</td>
<td>n/a</td>
<td>n/a</td>
<td>10.4</td>
<td>[8.6-12.2]</td>
<td>n/a</td>
</tr>
<tr>
<td>Clouse</td>
<td>1980-1994</td>
<td>100,000</td>
<td>39</td>
<td>AD</td>
<td>5.2</td>
<td>2.2</td>
<td>3.5</td>
<td>[2.4-4.6]</td>
<td>56</td>
</tr>
<tr>
<td>Mészáros</td>
<td>1972-1998</td>
<td>106,000</td>
<td>86</td>
<td>AD</td>
<td>n/a</td>
<td>n/a</td>
<td>2.95</td>
<td>2.4</td>
<td>n/a</td>
</tr>
<tr>
<td>Yu</td>
<td>1996-2001</td>
<td>22.9 mill.</td>
<td>5654</td>
<td>AD</td>
<td>n/a</td>
<td>n/a</td>
<td>4.3</td>
<td>80/90</td>
<td>66/72</td>
</tr>
<tr>
<td>Perko</td>
<td>1984-1993</td>
<td>n/a</td>
<td>170</td>
<td>TAA, TAAA, AD</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>62/35</td>
</tr>
<tr>
<td>Pressler</td>
<td>1969-1977</td>
<td>n/a</td>
<td>135</td>
<td>TAA, TAAA, AD</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>60/38</td>
</tr>
</tbody>
</table>

Abbreviations: TAA, Thoracic aortic aneurysm; TAAA, Thoracoabdominal aortic aneurysm; AD, Aortic dissection; n/a, not available

1 Including/excluding 30-day mortality
2 Surgical/palliative group
3 TAA/AD
4 8-year survival
Surgical treatment: rationale and indications

Indications for surgical treatment vary depending on the anatomy, pathology, and clinical presentation, but the fundament is to prevent or treat aortic rupture at the lowest possible surgical risk.

Type A aortic dissection

In acute type A dissection, surgery aims at saving the life of the patient by treating or preventing the lethal complications (1) aortic rupture with hemorrhage or tamponade, (2) coronary artery damage or compression with myocardial ischemia and (3) aortic valve detachment or compromise with (severe) acute aortic insufficiency and heart failure. The extremely grave prognosis outweighs the risk of acute surgery even in severely ill patients, and is since over two decades and still the treatment of choice for all patients with exception of the very old, moribund or severely brain damaged patients.

Chronic type A dissection is not common, but the dissected and spontaneously healed aorta tends to dilate over time, requiring surgery much in the same manner as an aneurysm.

Type B aortic dissection

In acute type B dissection, mortality is considerably lower and complications, although at times severe, less often life-threatening. Accordingly, surgery is avoided in the absence of uncontrollable symptoms (pain) or signs of rupture [26, 27]. Furthermore, percutaneous intervention has revolutionized the management of these patients [28-30]: visceral or lower extremity malperfusion can be treated by stent placement in compromised branches or by distal fenestration of the dissection membrane, allowing uninterrupted flow in both the true and the false lumen.

The placement of endovascular stent-grafts in the aorta, covering the intimal tear, dilated aortic segments or segments at risk of rupture is rapidly incorporated as an integral part of the management of acute type B dissection alongside with the mainstay of therapy, medical treatment of hypertension. Chronic type B dissection, prone to dilatation, is also target for endovascular treatment.

Thoracic and thoracoabdominal aortic aneurysms

Asymptomatic thoracic aortic aneurysms often grow by 0.1–0.5 cm/year [23-25]. According to the law of Laplace, increased diameter results in increased wall tension, and eventually the aortic wall will not withstand the strain and tear. Surgery aims to resect the aneurysm before rupture; indications based on maximal aortic diameters are referred above. In practice, maximal aortic
diameter on eg CT is used to establish indication for operation, see above. This simplification has obvious shortcomings: it does not apply to Marfan patients, it does not index aortic diameter to body size, and unique characteristics of the aortic wall predisposing of rupture are not accounted for.

In thoracoabdominal aortic disease, the risk of perioperative complications is indeed substantial. Spinal ischemic injury, respiratory failure, bleeding, gastrointestinal ischemia or renal failure occur in up to 50% [31]. Hence, thoracoabdominal aneurysms (TAAA) are approached surgically preferentially in the younger, motivated patient with gross and/or symptomatic dilatation of the aorta.

Notably, symptomatic aneurysms should be referred for surgery urgently irrespective of diameter. Manifestly ruptured thoracic aortic aneurysms are surgical emergencies, treated according to the same guidelines as given for acute dissections above.

Surgical treatment: outcomes

Short-term results
In studies on acute type A aortic dissection, the lowest 30-day mortality reported is 5.3% in 95 patients by Westaby [32]. Larger series, summarizing longer periods, typically report mortality in the 14–26% range [33-39]. From the multicenter, multinational IRAD collaboration, Trimarchi report an overall 25% mortality in 526 patients: 16.7% in stable and 31.4% in unstable patients [40]. In acute type B dissection, surgical mortality is even higher, 32–39% [37, 41, 42]. However, Reul report a decreasing surgical mortality, to 6.5% in selected patients, already in 1975 [43].

In studies of ascending aortic aneurysms or unselected thoracic aortic patient groups, early mortality vary from 1.7 to 15%, with a median of 9.4% [4, 38, 44-47]. In 832 patients operated in the descending aorta, Svensson report a 30-day and in-hospital mortality of 8% [48]. The same author, in an impressive series of 1509 thoracoabdominal aortic aneurysms, report a similar 8% 30-day mortality [49]. The report of 1220 TAAA patients from Houston presents an even lower 4.8% 30-day mortality [50]. The same group report discouraging figures with the use of hypothermic circulatory arrest (HCA) for TAAA repair: 29% 30-day mortality (elective cases 20%; acute cases 50%) [51]. For comparison, in a 65 year old male, predicted mortality by the logistic EuroSCORE is 26.8% in acute type A dissection with complications; 12.9% in uncomplicated acute type A dissection, and 6.8% in elective TAA repair [52].
**Cause of death**

Cardiac causes (infarction, left ventricular failure, arrhythmia) dominate, accounting for 21–52% of hospital deaths [34, 46, 53, 54]. Rupture is ascribed to 21–33% [33, 40], followed by stroke in 14–25% [33, 34, 40, 54], bleeding in 10–21% [33, 53, 54] and multisystem organ failure in 10–29% [33, 53, 54]. On the other hand, the IRAD group report 42% of early deaths as “unspecified” [40].

In an autopsy study, van Arsdell identify tamponade and rupture as major causes of death in non-operated patients, whereas brain injury and cardiac failure contribute 33% each of the surgical mortality [55]. Quite the same causes of death are reported for unselected patient-groups [4, 45, 46].

In the 30-year study by Fann et al, respiratory and renal failure, sepsis, and multisystem organ failure are relatively more common causes of death in patients operated in the descending aorta (acute and chronic type B dissections) [37].

**Risk factors**

In several reports, advanced age is associated with increased surgical mortality, as a continuous variable or defined as age above 60–70 years [33, 37, 38]. Preoperative hemodynamic compromise (including shock, cardiac tamponade, absence of hypertension and renal dysfunction) and concomitant procedures (predominantly CABG) are also identified as risk factors by several authors [33, 34, 37, 38, 40].

Risk factors associated with short-term surgical mortality in ascending aortic aneurysm patients are similar, with emphasis on age and reoperations but also cardiopulmonary bypass (CPB)-time and perioperative complications [4, 45, 46]. In descending and thoracoabdominal aortic disease, age, renal insufficiency, symptomatic aneurysm, and aortic cross-clamp time are associated with early mortality [48-50], and in a nationwide US study, hospital and surgeon volume were predictive of surgical mortality [31].

**Long-term results**

**Mortality**

In dissection type A, five-year survival is 52–89%, ten-year survival 37–56% and fifteen-year survival 24–46%, corresponding to a constant five-year attrition rate of approximately 10% [33, 34, 37, 39, 41, 54]. Yu et al, reporting from a large national Taiwanese database, present mortality rates of 66% at one year and 60% at five years: long-term mortality is more favorable in surgically treated patients compared to controls from the third year of follow-up [13]. They also compare survival to age- and sex matched healthy controls, with corresponding survival of 97% and 91%, respectively. In a New York material, five- and ten-year survival in discharged patients is 84%
and 64%, respectively, compared to an expected survival of 92% and 79%, respectively [33].

In type B dissections, long-term results are worse. In 46 operated patients, Fann reports five-, ten- and fifteen-year survival of 48%, 29%, and 11%, respectively [37]. Rizzoli, on the other hand, have comparable survival in type A and type B dissections (52% vs. 56%, 44% vs. 28% and 37% vs. 25% at five, ten, and fifteen years), but describe a different post-surgical hazard function in type B dissection, with an increase in hazard at approximately five years postoperatively not seen in type A dissections [41]. In a follow-up of 189 patients with type B dissection, the Stanford group compare medically treated (n = 122) and operated (n=67) patients. The long-term actuarial survival was similar in both groups: 60%, 35% and 17% at five, ten, and fifteen years [42].

In studies of ascending aortic aneurysms or mixed populations, five-year survival is 75%, ten-year survival 57–62%, and fifteen-year survival 33% [45, 47, 56]. Corresponding findings for descending aortic aneurysms are clearly worse: 82%, 60%, 38% and 22% at one, five, ten and fifteen years, respectively [48]. Follow-up is less extensive in TAAA cases, with 89% survival at one year, 88% at two years, 82% at four years, and 64% at six years [50].

Cause of death
Cardiac (25–32%), pulmonary (22–30%), cerebral (12–17%) and late aortic rupture (10–21%) are leading causes of long-term mortality [4, 18, 46, 57].

Risk factors
Among patient-related risk factors, advanced age, symptoms at presentation, angina, hypertension, and renal failure contribute to a worse long-term outcome [4, 36, 46, 58]. Earlier year of operation, use of composite graft, resection of the aortic arch, and inclusion rather than button technique for coronary artery transfer are procedure-related factors affecting long-term survival [4, 34, 45, 46, 59]. Postoperative complications (cardiac or renal failure, stroke, bleeding) also worsen long-term survival [34, 45, 46].

Surgical treatment: complications
The extensive surgical trauma, the prolonged period of CPB and often hostile patient characteristics including age, comorbidity, previous operations or severe hemodynamic compromise in emergency cases all contribute to the panorama of perioperative complications seen in thoracic aortic surgery. Cerebral complications are discussed below. Renal complications, including dialysis, occur in 4–9% [45, 47, 56, 60]. Respiratory complications requiring prolonged mechanical ventilation and/or tracheostomy occur in 5–42% [45,
Bleeding requiring reexploration is more common in acute dissections, 3–25% [44, 45, 47, 56] and multisystem organ failure is reported by Bachet to be 12% [39]. The dreaded spinal ischemic complications, resulting in paraplegia or paraparesis associated with descending and thoracoabdominal aortic replacement occur in 4.6–15% [48-51]. Pulmonary and renal complications are also more common after operations involving the descending and/or intraabdominal parts of the aorta [31, 61]

Cerebral complications
Cerebral complications (ie stroke and temporary neurological dysfunction, TND), are more common in operations for acute aortic dissection type A, especially when the arch is included in the disease and/or the repair. The incidence of cerebral complications is lower in other operations for TAD, but remains significantly higher than in most other cardiac operations. Results reflect case-mix, definitions, study period and methods. Furthermore, there is most probably a more-than-average positive publication bias, with selection of studies with favorable results, especially if associated with novel or innovative techniques.

Etiology and prevalence of cerebral complications
The etiology of cerebral damage in TAD operations varies. With HCA only, prolonged circulatory arrest produces intolerable general cerebral ischemia and time is limited. With femoral artery cannulation, retrograde embolization from an atherosclerotic thoracoabdominal aorta, or malperfusion due to cannulation of the false lumen and/or entry-reentry phenomena contributed to an increased frequency of cerebral complications [62, 63]. Antegrade cerebral perfusion may also produce or dislodge emboli or result in malperfusion. As summarized in table 2, in operations including the arch with some form of SACP, the median stroke rate is 5% (1.8–18.5%) and the median TND rate 5% (3.8–19%). For comparison, Ehrlich report 9% stroke (17% TND) with HCA+retrograde cerebral perfusion (RCP) in 54 patients [64], Svensson report 7% stroke in 656 patients managed with HCA alone [65], and Ergin 12% stroke (19% TND) in similar settings in 200 patients [38].

Prevention of cerebral complications
Strategies for preventing cerebral complications in surgery for TAD include

1 alternative cannulation sites
2 intraoperative cerebral monitoring
3 improved cerebral perfusion during HCA
4 improved perioperative diagnostic techniques (eg epiaortic ultrasound scanning)
The thesis focuses on strategies 1–3 that will be dealt with in detail, whereas 4–7 are beyond the scope of the text, and will not be discussed further.

Cannulation site
In elective operations, the distal ascending aorta is cannulated. Borger et al demonstrated almost a halving of cerebral microemboli as counted by TCD by placing the aortic cannula in the distal arch rather than in the ascending aorta in CABG patients [66]. With very few exceptions [54], cannulation of the ascending aorta is avoided in acute type A dissection, to preclude cannulation of the false lumen, entailing severe malperfusion.

Surgeons are gradually moving away from femoral artery cannulation. It may produce emboli and malperfusion, it can be thwarted by iliofemoral artery disease, and result in local complications (seroma, neuropathic pain, limb ischemia) [62, 63, 67]. Subclavian, axillary, or brachial artery cannulation may be more time-consuming, but often offers a disease-free vessel and antegrade flow [68-70]. The merits of subclavian artery cannulation are further discussed below.

Cerebral monitoring
Intraoperative cerebral monitoring includes electroencephalography (EEG) to verify electrical silence of the brain; transcranial doppler (TCD) to detect and quantify blood flow in the middle cerebral artery and/or microemboli occurring in this territory; jugular bulb venous saturation (SjvO2) as a measure of overall cerebral oxygen consumption, and near-infrared spectroscopy (NIRS) to monitor cerebral tissue oxygen saturation non-invasively. EEG and TCD require comparably large equipments and, more importantly, individuals to operate the equipment and interpret the results. Abandoning HCA alone as cerebral protection, the role of EEG is drastically diminished. Measuring SjvO2 is an invasive method. The catheter position needs to be confirmed to avoid spurious readings. An isolated cerebral territory may be ischemic without a reduction in overall saturation.

Near-infrared spectroscopy
Near-infrared spectroscopy (NIRS) is first described as a monitor of tissue saturation in the feline and human brain by Jöbsis in 1977 [71]. In the INVOS 4100 (Somanetics Inc., Troy, MI), light at two different, near-infrared, wavelengths (730 nm and 810 nm) are emitted from an LED-source and the
light reflected by tissues detected at two specified distances (fig. 1). Thereby the absorbance of light is determined. According to the Lambert-Beer law, the absorbance is proportional to the concentration of absorbing compounds [72]. For the wavelengths in use, light is absorbed almost exclusively by the oxygen-carrying (HbO) and oxygen-depleted (Hb) forms of the hemoglobin molecule, the chromophore with the highest absorption rate in the body [72-75]. The concentrations of the forms of hemoglobin can be expressed as oxygen saturation of the tissue monitored; the regional oxygen saturation (rSO₂) [74-76]. The equipment is user-friendly, comparably insensitive to ambient light and other circumstances, non-invasive, and measures rSO₂ in real-time with on-line monitoring.

The NIRS methodology used in healthy subjects for benchmarking of cerebral saturation is reported by Pollard [77]. The normal range vary inter- and intraindividually, with an average of 50–70% under normal conditions [71, 74, 77]. Equipments differ in algorithms, technical solutions and output, resulting in slight but measurable differences in rSO₂, rendering direct comparisons imprecise [78, 79]. Agreement with SjvO₂ vary with circumstances, and saturation values are not easily extrapolated or exchangeable [80, 81]. However, good correlation with functional MRI of the frontal cortex [82] and cerebral histopathology in experimental animals [83] is reported.

Potential drawbacks of the method include alleged monitoring of saturation of superficial (scalp, bone) tissues [75]; the INVOS device algorithmic assumption of a constant 75:25 proportion of venous to arterial blood in cerebral tissue despite a more dynamic and variable relationship [84], and the limited area of cortical tissue monitored. However, Kirckpatrick et al
find by preoperative angiography that the internal carotid artery supplies both the middle and anterior cerebral arteries in all patients. NIRS monitoring of the frontal lobe is therefore representative of all the internal carotid artery vascular territory [85].

**Determinants of rSO₂**

What determines cerebral tissue oxygen saturation in the clinical situation remains elusive. In a study of patients undergoing CABG, rSO₂ during CPB depends on pCO₂ whereas an alternative measure (oxidation state of mitochondrial cytochrome) correlated to Hb, temperature, pH and pCO₂ [86]. In experimental studies, the relation of rSO₂ to temperature and hematocrit is confirmed [87, 88]. Surprisingly, other studies fail to show correlation to mixed venous saturation [89] and arterial oxygen saturation [90], advocating a role for NIRS or other designated cerebral saturation rather than extrapolation from standard monitoring variables.

**Safe level of rSO₂**

In carotid artery surgery, two studies provide thresholds for “safe” drop in rSO₂ for instance at the application of vascular clamps: 16–18% [91] and 20–25% [85] respectively. No patient with less desaturation develops cerebral complications. In addition, hemispheric asymmetry of 25% or more implies an increased risk of cerebral ischemia [91]. In their experience with 101 patients undergoing aortic arch operations, Akashi report no stroke or TND when rSO₂ is maintained above 50% [92].

**rSO₂ monitoring of cerebral perfusion**

In studies of NIRS monitoring of patients undergoing selective antegrade cerebral perfusion (SACP) for operations involving the aortic arch, Orihashi and colleagues find a relationship between sustained desaturation (below 55%) and the development of cerebral complications but emphasize the difficulty of identifying embolic events and cerebellar ischemia with the method [93]. However, their report lacks multivariable statistical analysis of risk factors. Yamashita finds no difference in cerebral tissue saturation in 13 patients undergoing total arch replacement compared to 18 patients undergoing CABG and, more importantly, no relevant desaturation episodes in either group. Consequently, no patient suffer a stroke [94]. A third Japanese group report 13.6% cerebral complications in 66 patients. Only one stroke occur with normal rSO₂ levels; 17% of patients with temporary decline in rSO₂ are affected and 100% of patients with a sustained decline in rSO₂ develop stroke [95]. Finally, Akashi report increasing rSO₂ throughout SACP and lowered rSO₂ in two patients experiencing TND [92].
Cerebral perfusion strategies

The cerebral metabolic rate (CMRO₂) is inversely related to temperature and hence the tolerance for ischemia is increased at lower temperature. In the dog, CMRO₂ is reduced by 7% with 1°C reduction [96]. HCA elicit several pathophysiologic changes, including a generalized inflammatory response (neutrophil activation, degranulation and migration; complement activation, kallikrein and cytokine release; platelet degranulation and degradation); fibrinolysis and capillary leak [97], either as a direct consequence of hypothermia, or related to the prolonged time on CPB required for cooling and rewarming. The latter is restrained by gaseous microemboli formation at excess gradient between blood and heat exchanger and therefore time-consuming. Surgically, the HCA strategy offers the opportunity to avoid aortic cross-clamping if the hypothermia-induced fibrillating heart is decompressed by a vent. This could prove beneficial in cases of known atherosclerotic, dissected or otherwise diseased ascending aorta.

Hypothermic circulatory arrest

HCA as a cerebral protection strategy in thoracic aortic surgery was popularized by Griepp [98]. Analyzing outcomes in 200 patients 20 years later, the New York group reports a 15% in-hospital mortality, stroke in 11% and TND in 19% [38]. In multivariable analysis, duration of HCA was related to TND but not to stroke or mortality. Svensson et al report 12% in-hospital mortality and 7% stroke in 656 thoracic aortic operations utilizing HCA [65]. They establish 40 minutes at deep hypothermia (defined by EEG electrical silence rather than temperature; approximately 20°C in esophagus) as the “safe” limit. With HCA exceeding 40 minutes the risk of stroke increases; after 65 minutes mortality increases [65].

Though results are very similar, conclusions diverge: the New York group ascribes stroke to patient-related factors (causing emboli), not to duration of HCA. Paired with the concern that prolonged rewarming on CPB required with HCA increases total embolic load and that HCA alone does not offer flawless brain protection, their findings herald the advent of retrograde cerebral perfusion.

Retrograde cerebral perfusion

Retrograde cerebral perfusion through a cephalad cannula in the superior vena cava, as treatment of massive air embolism to the cerebral circulation during CPB, was introduced by Mills and Ochsner [99]. Taking the idea one step further, RCP was used as an adjunct to HCA in thoracic aortic surgery patients by Ueda and colleagues. In their first report on 8 patients, no death or stroke occurs [100]. Astudillo Ley describe stroke in 1/20 patients man-
aged with RCP and 11/40 patients without RCP (p < 0.05) for an overall stroke rate of 20% in aortic arch surgery [101]. A study comparing 54 patients managed with HCA and RCP to 55 historical controls managed with HCA alone finds lower mortality (15% vs. 31%), lower stroke rate (9% vs. 27%), and unaltered TND rate with RCP [64]. Seemingly, mortality and stroke rate in controls are unacceptably high and corresponding incidence with RCP approaching “normal”. In a 2002 review of 163 patients with acute aortic dissection, Bavaria and colleagues, utilizing HCA and RCP, present 10% in-hospital mortality and 3% stroke [102], providing strong clinical support for the efficacy of RCP.

However, only a few years after its initial appearance, several experimental studies question the alleged benefits of RCP. Several studies fail to show nutritive, capillary cerebral blood flow [103-107] and detect a substantial shunting away from the cerebral circulating through venous anastomoses and the azygos system [103, 106]. Further, uncertainty about optimal perfusion pressures and the risk of developing cerebral edema become evident [108, 109]. Currently, RCP is believed to supply some, largely non-nutritive cerebral blood flow that may improve cooling, and possibly aid in the evacuation of air and debris.

**Selective antegrade cerebral perfusion**

Direct perfusion of the cervical vessels during surgery on the arch is first performed by DeBakey [110] and Crawford [111]. With the occasional exception, stroke rate is a disappointing 25% [111]. The outcomes, and the obvious technical complexity including clamps, snares, cannulae and monitoring, make the concept largely obsolete. However, the appeal of orthograde cerebral blood flow at controlled conditions, the possibility of selective brain hypothermia with concomitant higher body temperature (thus obviating many of the disadvantages of HCA as mentioned above), and the development of surgical and perfusion techniques led to the reintroduction of SACP on a larger scale in the 1990’s by Bachet [112] and Kazui [113]. SACP gain popularity especially in complex total arch replacement, but soon engulf any thoracic aortic operation requiring an open distal anastomosis.

Several authors report outstanding results with SACP [114-116] but on average, outcomes are only slightly superior to those reported with previous techniques (table 2). Recent developments include cannulation of the right axillary or subclavian artery rather than direct cannulation of the innominate artery [68, 117, 118] thus removing one cannula from the surgical field and reducing arch vessel manipulation.
Comparing HCA, RCP, and SACP

The experimental and clinical documentation of HCA, its effect, merits, and drawbacks will be unparalleled for unforeseeable time. Very few studies compare the various cerebral perfusion strategies in a controlled, randomized fashion [119-121]. Harrington and associates, in two studies of neuropsychological outcome after aortic arch operations find no clinical benefit of adding RCP to HCA [119] or by using a SACP strategy [120]. However, the latter entail less deterioration in brain metabolism [120]. Svensson compare all of the three modalities (10 patients each and 5 CABG patients as controls) and find essentially no difference in clinical outcome or release of neuron-damage marker S100β [121]. To do studies of SACP justice, it needs to be pointed out that SACP time often by far exceed the “safe” limit of HCA (table 2), and therefore, in the mind of several authors, SACP add “the luxury of time” to the construction of the open distal anastomosis, at no added increment in stroke risk compared to HCA alone.

Several experimental studies in the pig find superior outcomes with SACP compared to HCA or HCA+RCP: postoperative behavioral scores are higher, dye and microsphere studies implicate superior perfusion distribution, and histopathological examination depict nuclear changes and apoptosis without SACP [122-124].
<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Case-mix</th>
<th>SACP strategy</th>
<th>SACP time</th>
<th>Mortality</th>
<th>Cerebral morbidity</th>
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<td>171</td>
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<td>106</td>
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<td>Innominate only 35%</td>
<td>50 min</td>
<td>8.5%</td>
<td>Stroke 5.4%</td>
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<td>Ohmi [126]</td>
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**Abbreviations**
- SACP, Selective antegrade cerebral perfusion
- TND, Temporary neurological dysfunction
- LCA, Left carotid artery
- LSA, Left subclavian artery
- RSA, Right subclavian artery
- RBA, Right brachial artery
Quality of life

Quality of life (QoL) is elusive, difficult to measure and quantify despite the intuitive understanding of the term. QoL is the result of interactions between physical and mental restrictions and the individual’s ability to cope with such restrictions [130-132]. To a degree, QoL will be unpredictable in the individual, but features common for individuals of a defined group will tend to affect their QoL in a similar manner.

The short-form 36 (SF-36) self-rated health questionnaire

Herein, the term QoL is restricted to self-reported, health-related QoL. The short-form 36 (SF-36) is a questionnaire developed to quantify QoL within these limitations [132, 133]. It has been tested on large populations of normal subjects as well as patients, and translated and validated in several languages including Swedish [131, 134]. The SF-36 does not contain disease-specific questions. To adequately describe a patient group an additional questionnaire or specific questions should be used to supplement the SF-36. On the other hand, the generic nature makes it possible to compare the scores between different patient groups and populations, with potential benefits for understanding the impact of the disease studied on the QoL.

Quality of life in cardiac surgical patients

Common cardiac operations, ie CABG and aortic valve replacement, are the most widely investigated and where the first to be studied from a QoL-perspective, along with cardiac transplantation. As would be expected, QoL improves substantially and lastingly in these patients, mainly due to the profound effect on symptoms, physical restrictions, and ability to work [135-138]. Conversely, patients subjected to prolonged intensive care or protracted recovery after operation fare worse [139, 140]. In older (>80 years) cardiac surgical patients several studies present compelling evidence of a gain in QoL with surgery [141-144]. More recently, reports of better QoL after mitral valve repair than after valve replacement introduce the QoL-concept as an argument for choice of treatment [145, 146].

For long, QoL after thoracic aortic surgery was uninvestigated. The proportion of emergency cases reduces the possibility of preoperative assessment for comparison. Additionally, with an aim of surgery to produce a live patient, QoL is naturally considered of secondary interest. There is, however, increasing interest in the QoL of these patients, primarily as an additional outcome measure in comparisons of different perfusion or treatment strategies [147, 148].
Aims of the thesis

The overall aim of the present studies was to use national registers and clinical investigations to characterize the population with thoracic aortic disease and to detail the outcomes of surgical treatment, with emphasis on cerebral complications and their prevention.

Specific aims were to:

Determine the incidence, time trends and overall prognosis of thoracic aortic disease in Sweden, especially in surgically treated patients,

Examine the results of surgical treatment for thoracic aortic disease over time in terms of short- and long-term mortality, and identify factors associated with unfavorable outcomes,

Investigate the effect of two different strategies of selective antegrade cerebral perfusion (unilateral and bilateral, respectively) on the surgical outcome in terms of in-hospital mortality and perioperative stroke,

Evaluate the feasibility and safety of a simplified cannulation technique of the right subclavian artery for selective antegrade cerebral perfusion,

Evaluate the clinical utility and diagnostic performance of near-infrared spectroscopy and its ability to predict stroke in patients undergoing selective antegrade cerebral perfusion in operations on the ascending aorta and arch,

Examine the correlations between regional cerebral saturation index as measured with near-infrared spectroscopy and standard intraoperative monitoring variables,

Investigate health-related quality of life after surgery for thoracic aortic disease, with special reference to anatomy and acuteness of the disease, the occurrence of major perioperative complications, and the presence of permanent physical dysfunction.
Patients and methods

Study design, subjects, and data collection

Study I–II included subjects nationwide. Patients in paper III–V were operated at the department of Cardiothoracic Surgery, Uppsala University Hospital.

Study I
Design nationwide population-based epidemiological study with long-term cross-sectional follow-up.
Subjects the study population consisted of all individuals diagnosed with TAD (thoracic aortic aneurysm or dissection) in Sweden 01/01/1987 – 31/12/2002. Individuals with diagnostic and/or procedural codes corresponding to TAD or operations for TAD during the study period were identified in the Swedish hospital discharge (HDR) and cause-of-death (CDR) registers.
Data collection after multiple-source retrieval and register cross-linking, data were stored in a designated data-base for statistical analysis.

Study II
Design nationwide population-based register cohort study with long-term cross-sectional follow-up.
Subjects the study population consisted of all individuals operated for disease in the proximal thoracic aorta (ascending aorta or aortic arch) reported to the Swedish Heart Surgery register 01/01/1992–31/12/2004.
Data collection the complete register data for all defined study subjects were cross-linked with HDR and CDR data and stored in a data-base for statistical analysis.

Study III
Design retrospective, non-randomized clinical study of consecutive patients in two groups.
Subjects during a 44-month period, 65 patients were operated on the ascending aorta and arch and managed with unilateral or bilateral selective antegrade cerebral perfusion. Patients managed with other means of cerebral
perfusion or with HCA alone were excluded, as were patients with femoral artery cannulation.

**Data collection** data were compiled from the departmental clinical database and from medical records and stored in a designated data-base for statistical analysis.

**Study IV**

**Design** retrospective, non-randomized clinical study of consecutive patients.

**Subjects** during a 20-month period, 46 patients undergoing surgery including arch procedures with SACP were monitored intraoperatively with near-infrared spectroscopy.

**Data collection** data were retrospectively collected from the departmental clinical data-base and from medical records. Data on rSO₂ and arterial blood gases were collected according to a pre-specified protocol identifying key events of the operation (fig. 2). Data were stored in a designated data-base for statistical analysis.

**Study V**

**Design** retrospective cohort study with medium- to long-term cross-sectional follow-up.

**Subjects** under a 5-year period, 115 patients underwent operations on the thoracic or thoracoabdominal aorta. At a median follow-up time of 26 months postoperatively, 81 were alive and eligible for study. QoL questionnaires were returned by 76 patients, forming the study population.

**Data collection** data were retrospectively collected from the departmental clinical data-base and from medical records. Questionnaire replies were stored in a designated data-base together with clinical data for subsequent statistical analysis.

*Figure 2. Sampling protocol for rSO₂ and arterial blood gas analysis in study IV*
Definitions

The classification and definitions of TAD have been described above (p. 10).

Mortality

In study I, 30-day mortality was used for simplification and coherence to similar studies. In study II, mortality within 60 days postoperatively was attributed to the operation, to adequately include late surgical complications including stroke, mediastinitis etc. Cause of death was procured from the CDR, based on primary (study II) or underlying (study I) diagnostic codes. In the clinical studies (papers III–V), short-term mortality was defined as in-hospital mortality, ie death of any cause prior to discharge from hospital. The common alternative measure, 30-day mortality, spuriously fails to attribute death in patients with long hospital stays to the operation [149]. Long-term mortality was defined as death occurring at any time beyond 30 or 60 days of diagnosis or operation, respectively.

Morbidity

In study II, the Swedish heart Surgery register definitions were applied. For common perioperative complications in study III–V simple definitions were used: bleeding=bleeding requiring surgical re-exploration; infection = superficial or deep wound infection requiring surgical revision; renal failure=need of dialysis occurring postoperatively; respiratory failure=need of prolonged (>72 hours) mechanical ventilation and/or tracheostomy.

Cerebral complications

Cerebral complications were divided into stroke and temporary neurological dysfunction (TND). The diagnosis of stroke was based on clinical findings: focal or global central neurologic deficit (eg hemi- or monoparesis, facial paresis, dysarthria or dysphagia or coma) not resolving before discharge and almost invariably corroborated by a neurologist opinion and/or CT of the brain demonstrating explanatory lesions. Neurological symptoms resolving spontaneously prior to discharge from the operating unit or judged as TND by a neurologist were classified as TND. The definitions reflect clinical stroke ascertainment and resemble the definitions proposed by eg the Cleveland Clinic [62].
Emergency, acute, and elective operations

Overall, operations performed within 24 hours of presentation were considered acute; otherwise operations were defined as elective. In study II, based on time elapsed from acceptance for operation, the terms emergency (≤24 hours or date of acceptance=date of operation), acute (≤14 days) and elective (>14 days) operation were used to allow a more granular separation of cases.

Surgical techniques

Below, the techniques used at the department of Cardiothoracic Surgery at Uppsala University Hospital, pertaining to study III–V, are described. Operations on the ascending aorta and aortic arch were performed almost exclusively through median sternotomy. Operations on the descending or thoracoabdominal aorta were performed through a left posterolateral thoracotomy with additional extension to the retroperitoneal space as necessary, typically by means of a paramedian laparotomy.

Aortic dissection

In aortic dissection, surgery aimed to replace the ascending aorta with resection of the intimal tear, often located at or below the sinotubular junction, and re-entries, often located in the arch.

The disease-free native aortic valve not irreparably damaged by the dissection was resuspended and preserved. If regurgitant by aortic dilatation, the sinotubular junction was downsized by the proximal, supracoronary aorta-to-graft anastomosis. Composite graft or prosthetic aortic valve replacement was generally avoided in acute aortic dissection, if not mandatory due to aortic valve disease, damage, or annular dilatation.

During hypothermic circulatory arrest, the arch was opened and inspected and the reentry excised if possible, often by a hemiarch replacement. Occasionally, additional procedures on the arch were performed; separate grafting of damaged cervical vessels or total arch replacement with or without construction of an elephant trunk.

Aneurysms of the ascending aorta

Similar principles as for aortic dissection were applied in resection of ascending aortic aneurysms. HCA was employed if warranted by the extent of disease – in a majority of cases the distal anastomosis was constructed proximal to the aortic cross-clamp.

Aortic root aneurysms were managed either by composite graft replacement with coronary button reanastomosis to the graft or by valve-sparing
root replacement using the techniques of David [150] or Yacoub [151]. Over
time, the David procedure has prevailed in non-aortic stenosis cases, and in
its most recent modification a graft restituting the aortic sinuses (Gelweave
Valsalva, Vascutek) has been used.

Aneurysms of the aortic arch
In extensive arch surgery, the entire arch was resected and replaced by a
tubular graft. If part of a generalized aortic dilatation, an elephant trunk was
created at the distal anastomosis for future use in distal aortic repair. Gener-
ally, the cervical vessels were saved on a common island of aortic tissue and
sutured en-bloc end-to-side to a corresponding opening in the graft.

Aneurysms of the descending and thoracoabdominal aorta
In descending and thoracoabdominal aortic disease requiring longer seg-
ments of aorta to be replaced, intercostals were oversewn if not deemed
critical for spinal cord circulation or if bleeding heavily. Intercostals at the
Th10–L2 level were generally anastomosed en-bloc end-to-side to the graft
to supply the spinal cord. Techniques for the reanastomosis of major in-
traabdominal arteries depended on anatomical and surgical circumstances.
Often, the celiac trunk, superior mesenteric artery and one renal artery could
be reattached en-bloc with an end-to-side graft anastomosis, whereas one
renal artery often was reattached by means of a small interposition graft.
Depending on the extent of aortic dilatation, the distal aortic anastomosis
was either end-to-end or by means of a bifurcation graft to each iliac artery.

Perfusion techniques
Right subclavian artery cannulation
During the time-span of the thesis, femoral vessel cannulation was gradually
replaced by right subclavian artery cannulation in cases involving an arch
procedure, including the majority of cases with acute type A dissection. The
artery was exposed through a 10 cm incision below the right clavicle. Fibers
of the pectoralis major muscle were spread, the underlying fascia incised and
the artery and vein identified. Vein tributaries were ligated if necessary. The
artery was mobilized and circled. If judged adequate in size and not seriously
affected by arteriosclerosis or dissection, an oval 5-0 prolene pursestring was
placed ventrally.

After heparinization, the centre of the pursestring was punctured and a
guide-wire introduced and often possible to visualize with transesophageal
echocardiography. A small arteriotomy was made and a thin-walled, flexi-
ble, wire-reinforced high-flow cannula negotiated into the vessel over the guide-wire and introduced a few centimeters into the artery. The cannula was checked for back-bleeding, de-aired, secured and connected to the arterial line. Size 18-24F Edwards EOPA or RMI FemFlex II cannulae were used.

Cardiopulmonary bypass
For elective proximal cases, regular ascending aortic and right atrial appendage cannulation with a two-stage cannula was employed. For CPB, standard roller pumps, hard shell venous reservoirs, and hollow-fiber oxygenators with or without heparin surface coating were utilized. Acid-base balance was maintained with the α-stat strategy. Patients were fully heparinized (300 U/kg) and full normothermic flow was calculated as 2.4×body surface area. On CPB, patients were cooled to deep (16º–19º C) or moderate (20º–26º C) hypothermia. The left ventricle was vented through the right upper pulmonary vein, avoiding cardiac distension on hypothermic ventricular fibrillation. Cold cardioplegia, crystalloid or blood, was infused repeatedly anterogradely or retrogradely depending on circumstances and surgeon preferences. To avoid intolerable alterations in hemodynamics, circulatory compromised patients were often cannulated and on CPB prior to anesthetic induction.

Perfusion strategies in descending aortic operations varied. At times, total CPB was used. More commonly, the segment to be resected was isolated between clamps and left heart bypass was employed with a draining cannula in the left atrium and a return cannula distal to the isolated segment, with a centrifugal pump providing flow and the lungs oxygenating the blood. Clamp-and-sew and HCA strategies, respectively, were used sparingly.

Selective antegrade cerebral perfusion
On reaching target temperature, with the arch dissected and the two proximal head vessels encircled with tape tourniquets, the head was packed in ice and CPB discontinued. After clamping the innominate artery proximally, unilateral SACP was begun through the right subclavian artery cannula at ~5 ml/kg/min. Either this set-up was used for SACP or, more often, a second cannula was introduced and secured into the left carotid artery, connected to the arterial line, and the flow rate increased to approximately 10 ml/kg/min. After tying down the distal anastomosis, with the patient in Trendelenburg position, the arch was carefully de-aired, facilitated by back-bleeding from the decannulated left carotid artery and the left subclavian artery. Thereafter, the graft was clamped proximal to the suture line, the innominate artery declamped, CPB restarted and rewarming begun. Cerebral perfusion pressure was not measured routinely, but was repeatedly found to be within the 40–70 mm Hg range when monitored in the left carotid artery.
Cerebral monitoring with near-infrared spectroscopy

The INVOS 4100 equipment was used for near-infrared spectroscopy. After a degreasing scrub, single-use, adhesive optical patches (SABF Adult) were placed bilaterally on the forehead according to manufacturer’s instructions to avoid the sagittal sinus, the temporal muscles and the frontal sinuses. Normally, the patches were applied soon after the induction of anesthesia, and the rSO2 values demonstrated in real-time and recorded on the patient’s anesthesia and/or perfusion chart. NIRS monitoring was discontinued at the end of operation.

Statistical methods

Data were collected from separate sources and stored in designated databases for work-up and statistical analysis. Parametric or non-parametric methods were chosen depending on study sample sizes and variable distributions. Accordingly, data were presented as counts with percentages or as either means with 95% confidence intervals (95% CI) or standard deviation (SD), or as medians with interquartile ranges (IQR). Two-tailed p-values < 0.05 were considered statistically significant.

Study I

Incidence, with gender separation, was calculated as unadjusted number of new (incident) cases yearly, with the national census and vital statistics providing an annually updated denominator. Incidence of operations was calculated in an identical fashion. For calculation of over-mortality associated with TAD, standardized mortality rates (SMR) were used, providing a comparison with an age- and sex-adjusted normal population. For risk comparisons, a Poisson-distribution of events was assumed and Poisson regression analysis used to calculate relative risks (RR). Factors associated with short- and long-term mortality were analyzed with Cox proportional hazards analysis to adjust for time-dependency [152]. Survival was estimated by the actuarial Kaplan-Meier method [153], with the log-rank test used for comparisons of survival curves. The Hosmer-Lemeshow test was used to evaluate regression models [154].

Study II

For descriptive statistics, parametric methods were used: means and standard deviations were calculated, and Student’s t-test and χ²-test were used for group comparisons. Factors associated with short- and long-term mortality were analyzed with Cox proportional hazards analysis to adjust for time-
dependency [152]. Accounting for different postoperative hazard phases, separate Cox analyses were performed for short-term (<60 days), intermediate-term (60 days–5 years) and long-term mortality. Survival was estimated by the actuarial Kaplan-Meier method [153], with the log-rank test used for comparisons of survival curves.

Study III

Sample size and variable distributions dictated the use of parametric statistical methods. Group comparisons were performed with Student’s t-test (continuous variables) or $\chi^2$-tests (categorical variables). To identify factors associated with perioperative stroke, mortality or adverse outcome (composite stroke or mortality end-point [117, 155]), variables with p-values $\leq 0.10$ in bivariate analyses were entered into separate forward logistic regression models.

To compensate for the non-randomized allocation of perfusion strategy (unilateral vs. bilateral), a matched case-control situation was created utilizing propensity score as a balancing score between groups [156-159]. In this setting, the propensity score corresponds to the probability of receiving a treatment given all known patient factors. Therefore, two patients with the same (or very close) propensity scores receiving different treatments could be considered as a matched pair with randomly (identical probability of) assigned treatment.

To construct the propensity score, all known, non-redundant variables were entered into a logistic regression equation solved for each patient. Patients from the two groups were paired according to their propensity scores with greedy matching, i.e., first patients with identical propensity scores were paired, followed by those with a 0.1 difference, and so on until all patients were pair-wise matched without overall group difference in propensity scores [156]. All patients (i.e., 17 from each group as 17 patients underwent unilateral SACP) were matched. Thereafter, group comparisons in the resulting case-control situation were performed (with non-parametric methods due to the reduced sample size): Mann-Whitney U-test for continuous variables and $\chi^2$ or Fisher’s exact test for categorical variables.

Study IV

Due to the limited sample size and skewed distributions in several variables, non-parametric statistical methods were used. Clinical data were presented as medians with interquartile ranges (IQR) or integers with percentages. Measurement data were presented as means with standard errors of the mean (SEM) as the variance of the point measurements was considered more relevant than the population variance. Groups were compared with the Mann-
Whitney U-test (continuous variables) or with \( \chi^2 \)-tests (categorical variables). Diagnostic performance indices were calculated as follows:

**Sensitivity** = true positives / (true positives + false negatives)

**Specificity** = true negatives / (true negatives + false positives)

**Positive predictive value (PPV)**

\[ \text{PPV} = \frac{\text{true positives}}{\text{true positives} + \text{false positives}} \]

**Negative predictive value (NPV)**

\[ \text{NPV} = \frac{\text{true negatives}}{\text{true negatives} + \text{false negatives}} \]

**Likelihood ratio positive (LR+)**

\[ \text{LR+} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} \]

**Likelihood ratio negative (LR-)**

\[ \text{LR-} = \frac{1 - \text{Sensitivity}}{\text{Specificity}} \]

These indices were all used to define the diagnostic properties and performance of rSO₂ measurements to define the ability of the method to accurately identify situations predictive of a perioperative stroke in the patients in study III. All calculations were performed after transforming crude rSO₂ data to change in percent relative to baseline, defined as rSO₂ measured during stable conditions on normothermic CPB.

The indices were calculated for optimal cut-off values as determined from the receiver operating characteristic (ROC) curve [160-163]. In the ROC curve, sensitivity was plotted against (1-specificity). A semi-parametric method (Analyse-It Software Ltd., Leeds, UK) was used to plot the ROC curve to illustrate the non-linear behavior of the measurements [164]. The area under the curve (AUC) in ROC analysis corresponds to the overall diagnostic capacity of the test [160, 161] and was calculated with the same semi-parametric method. The AUC vary from 1.0 (perfect test) to 0.5 (test equivalent to chance) [161, 162]. For clinical usefulness of a test, an AUC at least 0.75 is desirable [160, 165].

**Study V**

The SF-36 written generic health survey containing 36 questions with pre-specified multiple-choice answer options, resulting in a score of 0–100 (100 being highest) in eight so-called health dimensions was used. Survivors at the closing date of the study were identified and mailed the SF-36 health questionnaire and the specific questions along with instructions and a pre-paid return envelope. A reminder was mailed to non-responders after one month. For reliability, questionnaire response-rate needed to exceed 90% due to difficulties of imputing missing data. Missing data were replaced according to the SF-36 user’s manual [131]. Internal consistency of responses was determined by calculation of the Cronbach alpha coefficient [166].

Calculated group SF-36 scores were given as means with 95% CI. The absolute difference from the normal Swedish population [131], adjusted for
age and sex, was calculated. For group comparisons, non-parametric tests were used as above.

**Ethical committee approval**

Study I and II were approved by the regional ethics committee of Uppsala University. Study III–IV were approved after institutional board review but were not subjected to formal ethical committee approval due to the nature of the studies. Study V was approved after institutional board review but was not subjected to formal ethical committee approval in accordance with legislation and regulations at the time of the study.
Results

Incidence and operations

During the 16-year study period, 14229 individuals with a diagnosis of thoracic aortic disease were identified. 3190 subjects (22%) did not reach hospital alive, but had a diagnostic autopsy. During the study period, incidence increased significantly in both sexes. The increase was more pronounced in men, starting at 10.7/100 000 in 1987 and increasing 150% to 16.3/100 000 in 2002 (fig. 3). In women, incidence rose by 128% from 7.1/100 000 to 9.1/100 000 over the same time (fig. 3).

In Poisson regression analysis of incidence, the relative risk (RR) of thoracic aortic aneurysm or dissection was 137 [95% confidence limits 116–161] times higher in subjects 70 years or older compared to individuals <30 years. It was 2.2 [2.2–2.3] in men compared to women. The RR of a diagnosis of thoracic aortic aneurysm or dissection was 1.53 [1.38–1.70] in 2002 compared to 1987.

A total of 2455 operations on the thoracic aorta were performed 1987–2002. The annual incidence of operations on the thoracic aorta increased slowly in men from 0.8/100 000 in 1987 to 1.9/100 000 in 1996 and thereafter increased three-fold over a 5-year period to 5.6/100 000 in 2002 for an overall 7-fold increase (fig. 4). In women, a slower progress was observed, but overall the operative incidence increased 15-fold from 1987 to reach 3.0/100 000 in 2002 (fig. 4). For operations, the RR remained doubled in men, 2.4 [2.2–2.6] and rose sequentially over the study years to reach a high 8.1 [5.9–11.1] for 2002. Unlike the incidence, RR of operation peaked in the younger 60–69 years age group; 46.0 [35.8–59.0].

During the 1992–2004 period of study II, 2634 proximal thoracic aortic operations were identified in the Swedish Heart Surgery register. The characteristics of these patients are shown in table 3. Briefly, 68% were male, mean age was 60 (SD13) years, 1821 (69%) were operations for TAA and 813 (31%) operations for aortic dissection. In 1514 (59%) an aortic valve prosthesis was implanted, and 471 (18%) had concomitant CABG.
Figure 3. Incidence of thoracic aortic aneurysms and dissections in Sweden 1986-2002 (study I)

Figure 4. Annual number of operations for thoracic aortic aneurysm and dissection in Sweden 1986-2002 (study I)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=2634)</th>
<th>Aneurysm (n=1821)</th>
<th>Dissection (n=813)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n</td>
<td>1780 (67.6%)</td>
<td>1215 (66.7%)</td>
<td>565 (69.5%)</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>60 (13)</td>
<td>60 (14)</td>
<td>59 (12)</td>
</tr>
<tr>
<td>Age, range</td>
<td>9 – 87</td>
<td>9 – 87</td>
<td>14 – 85</td>
</tr>
<tr>
<td>Age 0 – 39 years, n</td>
<td>231 (8.8%)</td>
<td>173 (9.5%)</td>
<td>58 (7.1%)</td>
</tr>
<tr>
<td>Age 40 – 69 years, n</td>
<td>1676 (63.6%)</td>
<td>1109 (60.9%)</td>
<td>567 (69.7%)</td>
</tr>
<tr>
<td>Age &gt; 69 years, n</td>
<td>727 (27.6%)</td>
<td>188 (23.1%)</td>
<td></td>
</tr>
<tr>
<td>Op year 1992 – 1997, n</td>
<td>1003 (38.1%)</td>
<td>656 (36.0%)</td>
<td>345 (42.4%)</td>
</tr>
<tr>
<td>Op year 1998 – 2004, n</td>
<td>1631 (61.9%)</td>
<td>1165 (64.0%)</td>
<td>468 (57.6%)</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>66 (2.5%)</td>
<td>54 (3.0%)</td>
<td>12 (1.5%)</td>
</tr>
<tr>
<td>Reoperation, n</td>
<td>189 (7.2%)</td>
<td>137 (7.5%)</td>
<td>52 (6.4%)</td>
</tr>
<tr>
<td>CABG, n</td>
<td>471 (17.9%)</td>
<td>394 (21.6%)</td>
<td>77 (8.9%)</td>
</tr>
<tr>
<td>AVR, n</td>
<td>1514 (59.3%)</td>
<td>1231 (67.6%)</td>
<td>281 (34.6%)</td>
</tr>
<tr>
<td>Elective (&gt; 14 d), n</td>
<td>1260 (47.8%)</td>
<td>1184 (65.0%)</td>
<td>74 (9.1%)</td>
</tr>
<tr>
<td>Acute (&lt; 14 d), n</td>
<td>298 (16.4%)</td>
<td>126 (15.5%)</td>
<td></td>
</tr>
<tr>
<td>Emergency (&lt; 24h), n</td>
<td>580 (22.0%)</td>
<td>142 (7.8%)</td>
<td>438 (53.9%)</td>
</tr>
<tr>
<td>Unknown acuity status, n</td>
<td>370 (14.0%)</td>
<td>195 (10.7%)</td>
<td>175 (21.5%)</td>
</tr>
</tbody>
</table>

Surgical and short-term mortality

In study I (n=14229), unadjusted 30-day mortality was 6888/14229 (48%). For individuals diagnosed antemortally, 30-day mortality was 3698/11039 (34%). Mortality was higher for ruptured thoracic aortic aneurysms and dissections than for non-ruptured aneurysms (table 4). Age ≥ 60 years entailed increased 30-day mortality. Short-term mortality decreased for all subjects and operated subjects alike from 1995 and onwards compared to the 1987–1994 period. After operation, 30-day mortality was 7.6% for non-ruptured thoracic aortic aneurysms, 22% for aortic dissections, and 35% with thoracic aortic rupture. With operation, the nearly four-fold increase in mortality ensuing from rupture was decreased to 1.71.

In study II, overall surgical mortality (60-days) was 356/2634 (13.5%): 16.7% in the earlier era (92–97) vs 11.6% in the later era (98–04), p=0.0002. For TAA, surgical mortality was 174/1821 (9.6%); for aortic dissection it was 182/831 (22.4%). In the former, it decreased from 13.7% (92–97) to 7.2% (98–04), p<0.0001; in the latter it remained unchanged, 22.3% vs 22.4% (fig. 5). In the later era, use of HCA, total arch replacement, and concomitant CABG increased in both groups (table 5), whereas the use of composite grafts were reduced. The incidence of stroke and renal failure increased in aneurysm surgery; only the former in dissection. Mean age was higher in dissection patients operated in the later era (table 5).
Table 4. 30-day mortality and associated factors in all subjects and subjects operated for thoracic aortic aneurysm or dissection. Counts with percentages and odds ratio (OR) with 95% confidence limits (95% CL) in multivariable logistic regression analysis (study I)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 11039)</th>
<th>Operated (n = 2455)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-day mort.</td>
<td>OR [95% CL]</td>
</tr>
<tr>
<td>Male sex</td>
<td>2315 (33%)</td>
<td>1</td>
</tr>
<tr>
<td>Female sex</td>
<td>1383 (35%)</td>
<td>1.08 [0.98 – 1.19]</td>
</tr>
<tr>
<td>Age 0 – 29 years</td>
<td>20 (13%)</td>
<td>1</td>
</tr>
<tr>
<td>Age 30 – 39 years</td>
<td>34 (16%)</td>
<td>1.29 [0.67 – 2.48]</td>
</tr>
<tr>
<td>Age 40 – 49 years</td>
<td>95 (19%)</td>
<td>1.38 [0.78 – 2.45]</td>
</tr>
<tr>
<td>Age 50 – 59 years</td>
<td>266 (21%)</td>
<td>1.54 [0.90 – 2.65]</td>
</tr>
<tr>
<td>Age 60 – 69 years</td>
<td>649 (27%)</td>
<td>2.17 [1.28 – 3.69]</td>
</tr>
<tr>
<td>Age 70 – years</td>
<td>2634 (41%)</td>
<td>4.11 [2.44 – 6.94]</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>1651 (37%)</td>
<td>1</td>
</tr>
<tr>
<td>Non-rupt. aneurysm</td>
<td>454 (10%)</td>
<td>0.19 [0.17 – 0.21]</td>
</tr>
<tr>
<td>Ruptured aneurysm</td>
<td>1593 (71%)</td>
<td>3.84 [3.43 – 4.30]</td>
</tr>
<tr>
<td>1987 – 1990</td>
<td>876 (42%)</td>
<td>1</td>
</tr>
<tr>
<td>1991 – 1994</td>
<td>1006 (39%)</td>
<td>0.97 [0.85 – 1.11]</td>
</tr>
<tr>
<td>1995 – 1998</td>
<td>928 (31%)</td>
<td>0.71 [0.62 – 0.82]</td>
</tr>
<tr>
<td>1999 – 2002</td>
<td>888 (26%)</td>
<td>0.63 [0.55 – 0.73]</td>
</tr>
</tbody>
</table>

Another 85 patients died within a year from operation, yielding 1-year mortality of 13.0% in TAA, and 25.2% in dissection. The most common causes of death were cardiac (43%), aortic (14%), and cerebral (14%).

In Cox proportional hazards analysis of factors associated with surgical mortality in all patients, emergency status (HR 2.80) and postoperative renal failure (HR 2.45) were the most powerful predictive variables. The same pattern appeared for TAA, but in aortic dissection, concomitant CABG (HR 2.15) was the single most powerful predictor of short-term death.
Figure 5. Survival in patients operated for aortic aneurysm and aortic dissection in the early (1992 – 1997) and late (1998 – 2004) era of study II

Table 5. Changes across time in age, operative procedures, and major complications in operations for thoracic aortic aneurysms and dissections (study II).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>60 (14)</td>
<td>61 (13)</td>
<td>...</td>
<td>0.13</td>
</tr>
<tr>
<td>HCA, n</td>
<td>115 (17.5%)</td>
<td>289 (24.9%)</td>
<td>1.55 [1.22-1.98]</td>
<td>0.003</td>
</tr>
<tr>
<td>TAR, n</td>
<td>13 (2.0%)</td>
<td>134 (11.5%)</td>
<td>6.43 [3.60-11.5]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Composite graft, n</td>
<td>360 (57.4%)</td>
<td>577 (52.7%)</td>
<td>0.81 [0.66-0.98]</td>
<td>0.03</td>
</tr>
<tr>
<td>CABG, n</td>
<td>30 (4.6%)</td>
<td>293 (25.2%)</td>
<td>7.01 [4.75-10.4]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke, n</td>
<td>9 (1.4%)</td>
<td>67 (5.8%)</td>
<td>4.39 [2.17-8.86]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal failure, n</td>
<td>9 (1.4%)</td>
<td>39 (3.4%)</td>
<td>2.49 [1.20-5.17]</td>
<td>0.01</td>
</tr>
<tr>
<td>Dissection</td>
<td>n=345</td>
<td>n=468</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>58 (13)</td>
<td>60 (12)</td>
<td>...</td>
<td>0.02</td>
</tr>
<tr>
<td>HCA, n</td>
<td>144 (41.7%)</td>
<td>324 (69.2%)</td>
<td>3.14 [2.35-4.20]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TAR, n</td>
<td>9 (2.6%)</td>
<td>56 (12.0%)</td>
<td>5.07 [2.47-10.4]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Composite graft, n</td>
<td>142 (43.4%)</td>
<td>113 (25.2%)</td>
<td>0.45 [0.34-0.62]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG, n</td>
<td>7 (2.0%)</td>
<td>57 (12.2%)</td>
<td>6.70 [3.01-14.9]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke, n</td>
<td>18 (5.2%)</td>
<td>64 (13.7%)</td>
<td>2.88 [1.67-4.95]</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal failure, n</td>
<td>10 (2.9%)</td>
<td>24 (5.1%)</td>
<td>1.81 [0.85-3.83]</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Long-term mortality

In study I, 2066 subjects (84%) survived >30 days after operation. Long-term mortality was significantly increased in subjects >60 years. There was a trend of decreasing long-term mortality with later year of operation. Initial diagnosis did not influence long-term survival appreciably: Kaplan-Meier survival curves for non-ruptured aneurysm, ruptured aneurysm, and dissection are shown in figure 6. One- to 15-year survival is given in table 6. Leading causes of death were: aortic (39%), cardiac (23%) and malignancy (9.3%).

The overall Standardized mortality rate (SMR) was 2.88 [2.62–3.16] (table 7). As expected it was higher in younger patient groups and in women, but not significantly affected by diagnosis. During the entire 17 years covered by study II, 714 patients (27%) died, for an overall 23.5% TAA mortality and 35.2% dissection mortality (fig. 7). Leading causes of death were cardiac (33%), aortic (19%) and cerebral (12%). In Cox analysis, age was associated with long-term mortality regardless of diagnosis, HR 1.05 per one-year increment. Acute status (HR 1.5) was associated with intermediate-term mortality overall and in TAA but not for dissection, whereas postoperative stroke (HR 2.2) was associated with intermediate term death only in TAA patients, and dissipated after 5 years.

Figure 6. Actuarial (Kaplan-Meier) survival in all 30-day survivors with aortic dissection, non-ruptured aneurysm, and aneurysm (study I). Log-rank test p = 0.3
Table 6. Actuarial survival probability (30-day survivors) at 1, 5, 10, and 15 years (study I)

<table>
<thead>
<tr>
<th>Years</th>
<th>Aortic dissection</th>
<th>Non-ruptured aneurysm</th>
<th>Ruptured aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93% [91 – 95]</td>
<td>92% [91 – 94]</td>
<td>88% [82 – 92]</td>
</tr>
<tr>
<td>5</td>
<td>79% [75 – 83]</td>
<td>76% [72 – 79]</td>
<td>78% [70 – 84]</td>
</tr>
<tr>
<td>10</td>
<td>59% [52 – 65]</td>
<td>56% [50 – 62]</td>
<td>50% [34 – 63]</td>
</tr>
<tr>
<td>15</td>
<td>48% [37 – 57]</td>
<td>41% [32 – 50]</td>
<td>35% [17 – 54]</td>
</tr>
</tbody>
</table>

Overall and in TAA patients, operation during the later period of the study (1998–2004) was strongly associated with lower risk of mortality throughout all phases – HR 0.5 at 60 days and up to 5 years, and HR 0.3 after 5 years. This effect could not be detected for aortic dissection at any phase of follow-up (fig. 5).

Figure 7. Actuarial (Kaplan-Meier) long-term survival in 2634 patients operated for thoracic aortic aneurysm or dissection 1992 – 2004 (study II)
Table 7. Standardized mortality rates (SMR) in subjects surviving beyond 30 days of operation (study I)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n, exp.</th>
<th>n, obs.</th>
<th>SMR [95% CL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0 – 29</td>
<td>0.2</td>
<td>4</td>
<td>20 [5.4 – 51]</td>
</tr>
<tr>
<td>Age 30 – 39</td>
<td>0.6</td>
<td>7</td>
<td>12 [4.9 – 25]</td>
</tr>
<tr>
<td>Age 40 – 49</td>
<td>3.1</td>
<td>25</td>
<td>8.1 [5.2 – 12]</td>
</tr>
<tr>
<td>Age 50 – 59</td>
<td>15.6</td>
<td>60</td>
<td>3.8 [2.9 – 4.9]</td>
</tr>
<tr>
<td>Age 60 – 69</td>
<td>53.4</td>
<td>172</td>
<td>3.2 [2.8 – 3.7]</td>
</tr>
<tr>
<td>Age 70 –</td>
<td>79.6</td>
<td>171</td>
<td>2.2 [1.8 – 2.5]</td>
</tr>
<tr>
<td>Male sex</td>
<td>106.6</td>
<td>279</td>
<td>2.6 [2.3 – 2.9]</td>
</tr>
<tr>
<td>Female sex</td>
<td>45.8</td>
<td>160</td>
<td>3.5 [3.0 – 4.1]</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>50.7</td>
<td>143</td>
<td>2.8 [2.4 – 3.3]</td>
</tr>
<tr>
<td>Ruptured aneurysm</td>
<td>23.9</td>
<td>63</td>
<td>2.7 [2.0 – 3.6]</td>
</tr>
<tr>
<td>Non-rupt. aneurysm</td>
<td>83.8</td>
<td>248</td>
<td>3.0 [2.6 – 3.4]</td>
</tr>
<tr>
<td>TOTAL</td>
<td>152.4</td>
<td>439</td>
<td>2.9 [2.6 – 3.2]</td>
</tr>
</tbody>
</table>

Cerebral perfusion strategy and adverse outcomes

In study III, forty-eight patients (74%) underwent bilateral SACP and the remaining 17 (26%) unilateral SACP through the right subclavian cannula only. Clinical results are summarized in table 8. A postoperative stroke occurred in 9 patients (13.8%); 5 in the unilateral group (29%) vs 4 in the bilateral group (8.3%), p=0.045. In bivariate statistical analysis, EuroSCORE >8 (OR 1.4) and unilateral SACP (OR 4.6) were associated with postoperative stroke, but only unilateral SACP remained independently associated with postoperative stroke in multivariable logistic regression analysis, OR 6.6 [95% CI 1.2–36].

To further investigate the association between SACP strategy and stroke, accounting for the retrospective, non-randomized study design, propensity score analysis balancing patients with unilateral and bilateral SACP was performed. In the resulting pseudo-case control situation (n=17 in each group), all variables except for duration of SACP were closely matched by the propensity score balancing, and the difference between groups regarding stroke remained: 0/17 in cases with bilateral SACP vs 4/17 with unilateral SACP, p=0.045.
Table 8. Summary of patients and results in study III-V (means with 95% CL)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study III (n=65)</th>
<th>Study IV* (n=46)</th>
<th>Study V (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : Female ratio</td>
<td>49 : 16</td>
<td>31 : 15</td>
<td>53 : 23</td>
</tr>
<tr>
<td>Mean age (95% CI)</td>
<td>59 (56–62)</td>
<td>61 (53–67)</td>
<td>59 (56–62)</td>
</tr>
<tr>
<td>Acute (%)</td>
<td>42 (65 %)</td>
<td>23 (50 %)</td>
<td>41 (54 %)</td>
</tr>
<tr>
<td>EuroSCORE (95% CI)</td>
<td>9 (8–9)</td>
<td>9 (7–10)</td>
<td>n/a</td>
</tr>
<tr>
<td>Previous cardiac surgery (%)</td>
<td>8 (12 %)</td>
<td>n/a</td>
<td>13 (17 %)</td>
</tr>
<tr>
<td>Ascending aorta / arch (%)</td>
<td>65 (100 %)</td>
<td>46 (100 %)</td>
<td>62 (82 %)</td>
</tr>
<tr>
<td>CPB time (95% CI)</td>
<td>252 (232–273)</td>
<td>220 (192–286)</td>
<td>167 (149–184)</td>
</tr>
<tr>
<td>HCA time (95% CI)</td>
<td>38 (33–43)</td>
<td>38 (28–51)</td>
<td>n/a</td>
</tr>
<tr>
<td>SACP time (95% CI)</td>
<td>33 (29–37)</td>
<td>32 (25–46)</td>
<td>n/a</td>
</tr>
<tr>
<td>Bilateral : unilateral SACP</td>
<td>48 : 17</td>
<td>40 : 6</td>
<td>n/a</td>
</tr>
<tr>
<td>30-day mortality (%)</td>
<td>7 (11 %)</td>
<td>6 (13 %)</td>
<td>21 (18 %)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>9 (14 %)</td>
<td>6 (13 %)</td>
<td>16 (21 %)</td>
</tr>
</tbody>
</table>

* Median with IQR

The overall in-hospital mortality was 7/65 (10.8%); six deaths occurred in patients managed with bilateral SACP (12.5% vs 5.9%, p=0.67). Concomitant CABG and reexploration for bleeding were associated risk factors in bivariate analysis, but in multivariable logistic regression analysis, age >70 years (OR 12 [1.3–113]) surfaced as the only independently associated factor.

Right subclavian artery cannulation

Right subclavian artery cannulation was performed in 65 patients. In five cases (7.7%) cannulation-related technical problems occurred: cannula oversizing requiring replacement, inadvertent line clamping and subclavian artery injury in one each and cannula dislodgement or malpositioning in two. Only one case (1.5%), with arterial injury demanding interposition graft repair, was judged related to the cannulation technique per se. None of the 58 surgical survivors showed signs of impaired right arm circulation, nerve damage or local wound problems.
Near-infrared spectroscopy monitoring during cerebral perfusion

Near-infrared spectroscopy (NIRS) monitoring was undertaken in 46 patients undergoing operations including a period of hypothermic circulatory arrest with SACP (table 4). For analysis, crude measuring values were recalculated as percent change from baseline, relative rSO2. A common pattern of a slightly decreased rSO2 at the start of SACP, followed by a recovery to baseline during SACP and a compensatory increase to supra-baseline levels post-SACP during rewarming was observed. Overall, relative rSO2 was significantly higher in both hemispheres from the start of SACP to rewarming on CPB in patients without stroke (fig. 8). Similarly, rSO2 was higher in the unaffected hemisphere in stroke victims (fig. 9), and bihemispherically in patients managed with bilateral as compared to unilateral SACP (fig. 10). Due to few observations, the latter differences were not statistically significant.

Stroke and diagnostic performance of NIRS monitoring

Six patients (13.0%) suffered a stroke. Three (50%) were managed with unilateral SACP, and the time of HCA alone (without ongoing SACP) was significantly longer than in non-stroke counterparts, 16 (IQR 7–18) vs. 2 (0–10) minutes, p=0.004. The calculated cut-offs and diagnostic indices based on the recalculated monitoring data are presented in table 9. Sensitivity varied from 67 to 81%, specificity from 58 to 94% depending on laterality and time of measurement. The positive predictive value (PPV) reached a high 67% at the end of CPB, whereas the negative predictive value (NPV) remained stable at 93–97% throughout the procedure. At a relative rSO2 cut-off of 77–91% of baseline, the OR of postoperative stroke was 5.6–32 and the relative risk 4.6–13 (table 9). The ROC AUC was 0.72–0.87.

NIRS and standard intraoperative monitoring

Along with NIRS monitoring of rSO2, standard intraoperative monitoring variables were recorded: pH, pO2, pCO2, MAP and EVF. Generally, these variables did not differ between stroke and non-stroke individuals, and the correlations to simultaneous rSO2 were weak and non-significant (table 10).
Figure 8. Relative rSO$_2$ during SACP in patients with or without stroke. Left hemisphere (above) and right hemisphere (below), respectively (study IV)

Figure 9. Relative rSO$_2$ in stroke victims with right hemispheric stroke (above) or left hemispheric stroke (below), respectively (study IV)
Figure 10. Relative rSO₂ with bilateral and unilateral SACP, respectively. Right hemisphere (above) and left hemisphere (below), respectively (study IV)
Table 3. Diagnostic performance indices of right and left hemispheric relative rSO₂ values during and after SACP. Means with 95% confidence limits in brackets (study IV)

<table>
<thead>
<tr>
<th>SACP start</th>
<th>SACP mid</th>
<th>SACP end</th>
<th>Post SACP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROC area</td>
<td>0.87 [0.75 – 1.0]</td>
<td>0.75 [0.52 – 1.0]</td>
<td>0.79 [0.62 – 0.97]</td>
</tr>
<tr>
<td>Cut-off</td>
<td>81</td>
<td>76</td>
<td>87</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.83 [0.39 – 0.99]</td>
<td>0.83 [0.39 – 0.99]</td>
<td>0.60 [0.18 – 0.92]</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.78 [0.71 – 0.81]</td>
<td>0.81 [0.74 – 0.84]</td>
<td>0.89 [0.83 – 0.93]</td>
</tr>
<tr>
<td>PPV</td>
<td>0.39 [0.18 – 0.46]</td>
<td>0.42 [0.20 – 0.50]</td>
<td>0.43 [0.13 – 0.66]</td>
</tr>
<tr>
<td>NPV</td>
<td>0.97 [0.88 – 1.0]</td>
<td>0.97 [0.88 – 1.0]</td>
<td>0.94 [0.88 – 0.99]</td>
</tr>
<tr>
<td>LR+</td>
<td>3.9</td>
<td>4.4</td>
<td>5.2</td>
</tr>
<tr>
<td>LR-</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Abbreviations**

SACP, Selective antegrade cerebral perfusion; ROC, Receiver operating characteristic; PPV, Positive predictive value; NPV, Negative predictive value; LR+, Likelihood ratio (positive); LR-, Likelihood ratio (negative); OR, Odds ratio; RR, Risk ratio.

Cut-offs expressed as percent of baseline.
Table 4. Arterial blood gases, hematocrit, and mean arterial pressure in patients without and with stroke, and correlation with simultaneous rSO2 (study IV)

<table>
<thead>
<tr>
<th></th>
<th>No stroke</th>
<th>Stroke</th>
<th>p-value</th>
<th>r rSO2 right</th>
<th>r rSO2 left</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before CPB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39 (0.05)</td>
<td>7.37 (0.07)</td>
<td>0.58</td>
<td>-0.03</td>
<td>-0.18</td>
</tr>
<tr>
<td>pO2</td>
<td>11.3 (8.7)</td>
<td>12.8 (27.6)</td>
<td>0.21</td>
<td>-0.005</td>
<td>0.04</td>
</tr>
<tr>
<td>pCO2</td>
<td>5.29 (1.14)</td>
<td>5.12 (1.07)</td>
<td>0.63</td>
<td>0.17</td>
<td>0.26</td>
</tr>
<tr>
<td>EVF</td>
<td>38 (9)</td>
<td>36 (4)</td>
<td>0.30</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>MAP</td>
<td>84 (22)</td>
<td>63 (25)</td>
<td>0.08</td>
<td>0.30</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>On CPB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (0.08)</td>
<td>7.34 (0.19)</td>
<td>0.79</td>
<td>-0.23</td>
<td>-0.20</td>
</tr>
<tr>
<td>pO2</td>
<td>27.5 (10.2)</td>
<td>24.0 (17.2)</td>
<td>0.83</td>
<td>-0.23</td>
<td>-0.16</td>
</tr>
<tr>
<td>pCO2</td>
<td>5.29 (1.46)</td>
<td>5.05 (1.56)</td>
<td>0.28</td>
<td>0.37*</td>
<td>0.33*</td>
</tr>
<tr>
<td>EVF</td>
<td>26 (6)</td>
<td>24 (6)</td>
<td>0.33</td>
<td>0.27</td>
<td>0.28</td>
</tr>
<tr>
<td>MAP</td>
<td>55 (10)</td>
<td>50 (15)</td>
<td>0.83</td>
<td>-0.14</td>
<td>-0.17</td>
</tr>
<tr>
<td><strong>After SACP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.29 (0.15)</td>
<td>7.23 (0.18)</td>
<td>0.37</td>
<td>-0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>pO2</td>
<td>27.8 (12.0)</td>
<td>31.0 (8.4)</td>
<td>0.40</td>
<td>-0.39*</td>
<td>-0.44*</td>
</tr>
<tr>
<td>pCO2</td>
<td>5.48 (1.82)</td>
<td>6.10 (1.35)</td>
<td>0.13</td>
<td>0.16</td>
<td>-0.01</td>
</tr>
<tr>
<td>EVF</td>
<td>26 (6)</td>
<td>24 (6)</td>
<td>0.75</td>
<td>0.29</td>
<td>0.37*</td>
</tr>
<tr>
<td>MAP</td>
<td>50 (20)</td>
<td>50 (15)</td>
<td>0.59</td>
<td>0.27</td>
<td>0.33*</td>
</tr>
<tr>
<td><strong>End CPB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (0.07)</td>
<td>7.37 (0.11)</td>
<td>0.60</td>
<td>-0.06</td>
<td>0.13</td>
</tr>
<tr>
<td>pO2</td>
<td>23.6 (11.5)</td>
<td>32.4 (27)</td>
<td>0.15</td>
<td>-0.11</td>
<td>-0.20</td>
</tr>
<tr>
<td>pCO2</td>
<td>4.69 (0.49)</td>
<td>4.85 (0.84)</td>
<td>0.96</td>
<td>-0.02</td>
<td>-0.24</td>
</tr>
<tr>
<td>EVF</td>
<td>27 (4)</td>
<td>27 (5)</td>
<td>0.73</td>
<td>0.06</td>
<td>-0.06</td>
</tr>
<tr>
<td>MAP</td>
<td>60 (9)</td>
<td>55 (10)</td>
<td>0.24</td>
<td>-0.03</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Post CPB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39 (0.08)</td>
<td>7.39 (0.05)</td>
<td>0.26</td>
<td>-0.18</td>
<td>-0.30</td>
</tr>
<tr>
<td>pO2</td>
<td>14.9 (12.3)</td>
<td>19.3 (8.3)</td>
<td>0.21</td>
<td>0.35</td>
<td>0.20</td>
</tr>
<tr>
<td>pCO2</td>
<td>4.90 (0.93)</td>
<td>5.16 (0.49)</td>
<td>0.26</td>
<td>0.18</td>
<td>0.11</td>
</tr>
<tr>
<td>EVF</td>
<td>30 (7)</td>
<td>30 (8)</td>
<td>0.78</td>
<td>0.24</td>
<td>0.11</td>
</tr>
<tr>
<td>MAP</td>
<td>64 (10)</td>
<td>63 (14)</td>
<td>0.94</td>
<td>0.05</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Abbreviations**
- CPB, Cardiopulmonary bypass; EVF, Erythrocyte volume fraction (%); MAP, Mean arterial pressure (mm Hg).
- Correlation (r) expressed as Spearman’s correlation coefficient.
- Values of pO2 and pCO2 given as kPa. To obtain mm Hg, multiply by 7.500
- *p-value for correlation < 0.05

**Quality of life after thoracic aortic operations**

Study V included a cohort of 115 patients operated in the thoracic or thoracoabdominal aorta. At cross-sectional follow-up a median of 26 months postoperatively, 76 of 81 (94%) of survivors participated in a health-related QoL survey (table 4). The patients scored lower than the sex- and age-adjusted average Swedish population in all the eight dimensions of the SF-36.
health questionnaire except for bodily pain (table 11). Meanwhile, 66% reported an improved perception of their health; 82% had in their opinion preserved or improved QoL and 91% described their operation as successful. In all subgroup comparisons, variations were considerable and no statistically significant intergroup differences.

Patients operated acutely had overall marginally lower SF-36 scores than patients operated electively (fig. 11). Scores were almost identical for patients undergoing ascending aortic and aortic arch procedures, but patients operated on the descending or thoracoabdominal aorta scored apparently lower in all dimensions except for general health (not shown).

Quality of life in patients with complications and late dysfunction

Patients suffering a major perioperative complication (reexploration, stroke, prolonged stay in ICU, n=17) reported somewhat lower SF-36 scores at follow-up (fig. 12). Role functioning, social functioning and mental health were the dimensions most affected (again, differences were not statistically significant). As expected, SF-36 scores were generally lower in individuals with persisting severe dysfunction (n=13), with a nearly linear relationship between degree of dysfunction and QoL scoring. Interestingly, the differences in mental health and social functioning were negligible despite severe or mild dysfunction (fig. 13).

Table 5. Mean SF-36 scores in eight dimensions for patients in study V with difference from age- and sex-adjusted normal population and Cronbach’s alpha coefficient for internal consistency (study V)

<table>
<thead>
<tr>
<th>SF-36 Dimension</th>
<th>Mean score [95% CL]</th>
<th>Diff. from norm [95% CL]</th>
<th>Cronbach α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodily pain (BP)</td>
<td>70 [63 – 77]</td>
<td>0.1 [-3.4 – 3.6]</td>
<td>0.97</td>
</tr>
<tr>
<td>Mental health (MH)</td>
<td>72 [68 – 78]</td>
<td>8.3 [5.7 – 11]</td>
<td>0.85</td>
</tr>
<tr>
<td>Vitality (VT)</td>
<td>58 [52 – 63]</td>
<td>9.5 [6.7 – 12]</td>
<td>0.77</td>
</tr>
<tr>
<td>Social functioning (SF)</td>
<td>77 [71 – 83]</td>
<td>10 [6.9 – 13]</td>
<td>0.80</td>
</tr>
<tr>
<td>General health (GH)</td>
<td>59 [54 – 64]</td>
<td>11 [8.5 – 14]</td>
<td>0.80</td>
</tr>
<tr>
<td>Physical functioning (PF)</td>
<td>63 [56 – 69]</td>
<td>17 [13 – 20]</td>
<td>0.92</td>
</tr>
<tr>
<td>Role emotional (RE)</td>
<td>60 [50 – 71]</td>
<td>21 [15 – 26]</td>
<td>0.91</td>
</tr>
<tr>
<td>Role physical (RP)</td>
<td>43 [32 – 54]</td>
<td>30 [25 – 36]</td>
<td>0.95</td>
</tr>
</tbody>
</table>
Figure 11. SF-36 scores for acute and elective patients. Means with 95% confidence limits (study V)

Figure 12. SF-36 scores in patients with or without major perioperative complication. Means with 95% confidence limits (study V)
Figure 13. SF-36 scores in patients with persistent severe or mild physical dysfunction compared to patients without persistent physical dysfunction. Means with 95% confidence limits (study V)
Discussion

Issues in register-based research

The unique personal identification number for every Swedish resident provides a basis for efficient, comprehensive and reliable register studies including cross-linking procedures. By the universally employed codes for diagnoses and procedures (ICD and NCSP, respectively), a wealth of information can be retrieved. However, the CDR and HDR are administrative registers, not emanating from clinical needs. In fact, such registers are often designed to minimize data content, to serve its primary purposes without generating an overflow of data [167]. As a corollary, its completeness, variability, accuracy and contents can all be questioned [167]. According to a recent report, completeness is very high (95–100%) and geographical variability very small in the HDR [5]. In both registers, accuracy is also reported as very high [5, 7]. The quality of the clinical content remains debatable.

There are no reports on the validity or reliability of the diagnosis or the accuracy of diagnostic coding of TAD (thoracic aortic aneurysms or dissections). Assumingly, (1) given the comparably clear diagnostic criteria and the well-recognized gravity of the conditions, over- and under-usage of diagnostic codes for thoracic aortic disease is uncommon. (2) There is a possibility of misclassification between thoracic aortic aneurysm, ruptured thoracic aortic aneurysm, and aortic dissection. In part, because of the often co-existing conditions of dissection and rupture (were dissection is a correct etiological diagnosis whereas rupture is a correct clinical diagnosis), in part due to the often used misnomer “dissecting aneurysm” that does not adequately describe the condition. (3) There is a possibility of inadequate intervention coding, related to a) ambiguous descriptions of interventions in the coding text, b) a tendency to oversimplify complex procedures and leave out relevant codes, c) local and personal traditions and rationing of codes. (4) Internationally, ICD-9 still dominates in registers and register-based research. The ICD-9 is much less detailed, and its use renders comparison more difficult. For all these reasons, findings in register studies must be cautiously interpreted.

In preparation for study II, the data quality and validity of the Swedish Heart Surgery Register was thoroughly evaluated. It is beyond the scope of this thesis to elaborate on the evaluation methods and the findings in detail, but overall validity was found to be satisfactory, comparable to that of other
similar registers [168-170] and certainly allowing a meaningful statistical analysis of the Register patient cohort.

The paucity of data remains the largest disadvantage of register studies. In study I, no variables related to medical history, diagnostic methods, medical therapy or surgical treatment except for prosthetic valve replacement could be included in the analysis. In study II, variables in the Swedish Heart Surgery register were available for analysis, but still several variables of potential importance for outcome were not included, eg major comorbidity (apart from previous coronary interventions, heart operations and dialysis), extent of aortic dissection and use of HCA, RCP or SACP. On the other hand, the included variables age, sex, acuity, reoperation, treatment era, major surgical procedures and postoperative complications have repeatedly had the greatest predictive power in similar studies [18, 33, 37, 44, 47, 171].

Evaluating surgical outcomes

The conditions for reporting surgical outcomes in TAD are suboptimal. Even large centers operate only about 20 cases of acute type A dissection annually. In consequence, reported patient populations are often mixed, including acute and chronic conditions, arch repairs, descending and/or TAAA cases and so on. Long-term results are often statistically questionable: at fifteen to twenty years even the largest studies only includes a handful of patients at risk, and a very small number of events.

Different definitions, even of “simple” events as death [149] and stroke [62, 155, 172], are abundant. The use (or misuse) of variables studied varies – the IRAD investigators include 290 variables per patient, yet fail to present data on long-term outcomes [40].

There are many pitfalls in determining long-term outcomes and its evolution over time. First, what is long-term outcome? In the surgical context, five or even ten years may not be “long-term” whereas it may seem far-fetched to link events very remote from an index diagnosis or operation to its occurrence. Second, all areas of medical care have improved over the past decades, implying that long-term outcomes would too. Third, case ascertainment and indications for operation have evolved; perhaps not even in a linear fashion. From strict diagnostic and surgical criteria creating few, selected surgical candidates with potential excellent outcome, to a much larger case-load and expanding indications based in part on the assumption that previously successful results can be extrapolated to a constantly sicker, older patient population. Finally, in statistical analysis, comparison of groups with different lengths of follow-up is problematic and sometimes violating the assumptions of standard methods or producing spurious results.
Is the incidence of thoracic aortic disease increasing?

In study I, data from a large, population-based, nationwide cohort with 16 years of observation were collected. A large and statistically significant increase in incident cases over the study period was found in both sexes (fig. 3). Incidence figures for 2002 were the highest yet reported in the literature. Except for one early study describing a decreasing trend in TAD incidence [10], subsequent reports are coherent in their findings of increasing number of annual cases [11-13]. However, there are no reports from population-based screenings for TAD, and methods of diagnostics, case ascertainment, case-mix, denominator estimations and format of reporting vary considerably [10-13, 21, 173]. Hence, there are not sufficient data to infer a true increase in disease incidence. There was certain evidence to say that an increasing number of cases were discovered annually, presenting health and welfare systems with an increased burden of patients requiring surgical treatment and/or regular and prolonged clinical and radiological follow-up, with attending consequences for resource allocation and implementation of management guidelines. Annual number of operations was also increasing (fig. 4), however with a more pronounced development in women, reflecting a more active surgical approach well justified by similar outcomes between sexes.

Are the results of surgical treatment improving?

In aortic dissection, results of treatment have improved dramatically compared to the era of conservative (medical) treatment [174] and compared to pioneering surgical attempts [110, 175]. Some outstanding results (5–15% surgical mortality) have also been reported recently [32, 33]. However, several authors report surgical mortality close to 20% in the current era [40, 53, 176, 177]. In the mind of Bachet, we cannot reach much further [178]. For thoracic aortic aneurysms, few authors claim operative deaths <5% [44] despite the elective nature of surgery.

In study I, RR for 30-day mortality in TAD decreased significantly over time, to reach a low 0.5 in the 99–02 period. Overall mortality was 22% in dissection, 35% in aortic rupture, and 7.6% in elective aneurysm operations: comparable to contemporary results in similar settings [13, 40, 177].

In study II, 60-day mortality after surgery for type A aortic dissection was 22%, and for proximal thoracic aortic aneurysm 8.0%. Results were significantly better in the recent 98–04 era compared to 92–97 (HR 0.3–0.5). Disappointingly, this finding was restrained to TAA operations (fig. 5). The most plausible explanation was an increasing proportion of older, complicated high-risk patients among type A dissections due eg to wider indications for surgery in the later era (table 5). However, a similar pattern was
obvious for patients with thoracic aortic aneurysms, leaving this finding partially unexplained.

**Is long-term survival in thoracic aortic disease improving?**

Agreeing that the ultimate aim of surgery is to restore life expectancy, successful operations would produce patient cohorts with attrition rates similar to that of the normal population. In reality, as previously reported [13, 33, 42], this is not the case. In study I, an overall SMR of 2.9 in individuals operated for TAD and somewhat higher (3.3) in unoperated patients was found. Attrition rates of close to 20% for each 5-year interval indicated that patients go on to succumb from TAD even fifteen years from their diagnosis or operation (study I–II). Whether this reflects pathophysiological properties of the diseases, reluctance to reoperate, suboptimal medication schemes, or failure of surveillance can be disputed. Nonetheless, it seems clear that further improved long-term outcomes require closer and longer follow-up and an active approach to reintervention – hopefully facilitated by the advancement in stent-based therapy for TAD.

In study I, a significant trend towards improved long-term survival was detected (p=0.014). In study II, surgical (HR 0.4) and long-term (HR 0.3) survival for the more recent surgical cohort was apparent. Importantly, this effect was not only related to improved short-term survival, but it only pertained to patients operated for thoracic aortic aneurysms. Thus, TAA surgery (mainly elective) has improved substantially in less than a decade, but surgery for aortic dissection (mainly acute or emergency) has not to a similar extent. On the other hand, long-term survival in study II (in dissection 75%, 70%, and 65% at 1, 5, and 10 years) compared favorably to virtually all other similar reports, with 10-year survival of 32–56% [13, 18, 33, 34], supporting the case for continuous improvement in surgical results across time.

**Do register studies contribute to improved outcomes?**

Identifying the nature of disease is always a prerequisite to tailor treatment and management. Epidemiology provides information on this nature in terms of how often, where, and in whom disease strikes. Summarizing the findings of study I–II (register studies rather than pure epidemiological studies), it was evident that surgical treatment was an overall more favorable option to achieve short- as well as long-term survival; at any rate, it was not a harmful strategy. Further, it was clear that patients were not cured by operation and needed ongoing follow-up to avoid premature death. From these data, it was
not possible to pin down exactly how intensified follow-up can lead to improving outcomes, but important information was provided that it must be improved not to waste the benefits of a successful operation. Study II showed that apart from increasing age (HR ~2.1 for a 15-year increase) not many risk factors for late death could be identified – indirectly suggesting surgery as early as possible. Study I–II provided a rationale for an active surgical approach and intensified postoperative surveillance, by pointing at improved results of surgery and constant postoperative attrition not attributable to specific, modifiable risk factors.

The findings of study II of cardiac and cerebrovascular causes for late death in 45% may also indicate room for improvement in the management of ischemic heart disease, heart failure, arrhythmia and antithrombosis: common and important causes of death not to be neglected in this population.

The incidence and prognosis of TAD presented in study I do not justify dedicated screening programs in the current context of restricted resources, awareness of cost-containment, and with available diagnostic methods. However, with extended screening efforts for abdominal aortic aneurysms, there are reason to believe that an additional number of multiple and/or thoracoabdominal aneurysms will be detected, and that new knowledge will generate that may identify high-risk groups that may benefit from screening for TAD.

Prevention of cerebral complications by improved cerebral perfusion?

In study III, the hypothesis of superiority of bilateral over unilateral SACP in terms of perioperative stroke and mortality was tested. This was a small, retrospective clinical study including a mixed patient population. They had in common a procedure involving the arch managed with SACP during HCA. The groups were comparable at baseline, and perioperative stroke was more common after unilateral SACP whereas death and adverse outcome (stroke or death) were not significantly different. In addition to the group comparisons, unilateral SACP surfaced as the single important risk factor for stroke in multivariable logistic regression analysis (OR 6.6). In interpreting the results of study III, the limitations of the study design must be kept in mind. The results (11% overall in-hospital mortality; 14% stroke [8% with bilateral SACP]) were not per se indicative of the superiority of SACP, but were a realistic outcome of a mixed population, and reflected an era of introduction of the method, with its attending learning-curve.

Study III was not undertaken to investigate the etiology of stroke. However, cerebral CT in stroke victims showed evidence of left hemispheric watershed-infarctions in two patients, indicating contralateral hypoperfusion in unilateral SACP. Conversely, stroke after bilateral SACP was uniformly
right hemispheric, suggesting embolic or malperfusion origin. Finally, the cannulation technique employed in study III proved reproducible, effective, and safe – it compared favorably to other reported techniques of direct [117] or side-branch [68, 179] cannulation of the right subclavian artery. Study III contributed to the concept of bilateral SACP; it entailed fewer strokes than unilateral SACP without apparent disadvantages, and the overall rate of TND was a very low (4.6%). It also confirmed the benefits of perfusion via the right subclavian artery. However, study III left questions of perfusion conduct and potential risks of full antegrade flow unanswered; these warrant further studies.

Advocates of unilateral SACP list simplicity, and sufficient left hemispherical perfusion through collaterals in the circle of Willis as merits. More importantly, they at times produce good clinical results, 0–2% stroke rate in limited studies [69, 70, 180]. Most authors, however, seem to overcome the obstacles of additional cannulae in the surgical field to achieve a more physiological brain perfusion with ensuing excellent results [114, 116]. The only previous study comparing unilateral and bilateral SACP in a similar patient group finds unilateral SACP to be the strongest predictor of in-hospital mortality (OR 0.08), whereas neurological outcomes are overall few and not significantly different [118].

In the acute setting, retrograde arterial perfusion through a femoral artery (FA) cannula has been the mainstay for decades. However, several authors find higher mortality [127], higher incidence of malperfusion [67], and worse neurological outcomes [62] with this strategy and, judging from presentations at the biannual Aortic Surgery Symposium in New York [181, 182], its importance is likely to be further diminished by increased use of subclavian artery cannulation.

It is more than 50 years since Seldinger published the simple, ingenious technique for catheter replacement over a guide-wire [183]. The technique is universally used; femoral artery cannulation for CPB is no exception. Nevertheless, described techniques for subclavian or axillary artery cannulation has hitherto used direct cannulation with an angled-tip cannula [117] or by means of an end-to-side anastomosed vascular graft [68, 179]. Neither technique seems superior to the Seldinger method, which in turn is simpler and faster without obvious major disadvantages.

**Prevention of cerebral complications by cerebral monitoring?**

In study IV, intraoperative, non-invasive, real-time monitoring of regional cerebral tissue oxygen saturation (rSO₂) with NIRS was employed in 46 patients. The study hypothesis was that NIRS monitoring of rSO₂ could ade-
quately identify harmful episodes of cerebral tissue desaturation and predict neurological outcome, ie perioperative stroke. Introduced in 1977 [71], NIRS is not a new method. It has gained popularity in cardiac surgery in the recent years, primarily in operations requiring HCA and/or cerebral perfusion [93, 95, 184]. Nevertheless, no previous study has focused on investigating the performance of NIRS as a diagnostic tool in the clinical situation, and therefore its use so far cannot claim to be evidence-based.

NIRS data on rSO₂ from critical phases of the operations (fig. 2) were collected retrospectively, together with simultaneous standard intraoperative monitoring data (arterial blood gases, hematocrit, and mean arterial pressure). From collected data, receiver operating characteristic (ROC) curves were constructed, as a measure of overall diagnostic performance (equal to the area under the curve) and as a means of identifying adequate cut-off values for calculation of diagnostic indices. As shown in table 9, multiple measurements from both hemispheres resulted in a wealth of information that can be summarized:

- The overall diagnostic performance of rSO₂ monitoring to predict stroke was acceptable for clinical standards, with a median ROC AUC of 0.78,

- Sensitivity (median 82%) and specificity (median 80%) were comparable, and NPV (93–97%) was higher than PPV (21–67%), indicating that episodes of low rSO₂ associated with stroke risk are seldom missed, at the cost of a definite number of false positive indications,

- The cut-off values in terms of relative decrease in rSO₂ were 76–91%, and at these levels of rSO₂ the OR of stroke increased to 5.6 to 32.

For a monitor of cerebral saturation, avoiding false-negative readings (ie undetected cerebral desaturation) would have top priority; according to the NPV, this was the case in 93–97%. As for ascertainment of cerebral desaturation, the LR⁺ of 1.9–11.3 (median 4.2) indicated that the likelihood that a patient with a positive test result (ie below specified cut-off) had relevant cerebral desaturation was 1.9–11.3 times higher than had it not. For comparison, LR⁺ is reported to be 11.2 for ST-segment changes on ECG and acute myocardial infarction [185], 6.3 for point-of-care TroponinT-test and acute myocardial infarction [186], and 2.0 for D-dimer analysis in asymptomatic patients with deep vein thrombosis [187].

As shown in figures 8–10, relative rSO₂ were lower in both hemispheres in stroke victims and it tended to be lower bilaterally with unilateral SACP and in the affected hemisphere in stroke victims. Finally, standard intraoperative monitoring variables correlated poorly with rSO₂ and did not differ between stroke and non-stroke subjects.
In all, the findings of study IV were in accordance to previous reports [85, 92, 93, 95], and provided evidence for a relationship between reduced cerebral tissue oxygen saturation and perioperative stroke, and that monitoring with NIRS can help identifying this condition, in contrast to standard monitoring. It takes further studies to apply this concept and to show that intraoperative manipulations and counteractions (of flow, pressure, temperature, cannula adjustments and so on) based on rSO\textsubscript{2} data actually can decrease the stroke rate after aortic arch surgery.

**Quality of life after all?**

Operations on the thoracic aorta are undertaken to preclude or treat immediately life-threatening aortic rupture. In the former, operative survival is assumed, and improved long-term survival the realistic goal. But probably not at any cost; surgery could be questioned did it not improve or at least preserve QoL [188]. Physical and emotional dysfunction often affects QoL, but not always predictably [130]. Consequently, major complications related to surgery, eg stroke, mediastinitis, renal impairment – especially if causing permanent dysfunction – would affect QoL, but so would effects of age, chronic disease and psychosocial factors [130, 189].

In study V, current health-related QoL was assessed by the SF-36 generic questionnaire. The SF-36 was insensitive to recall bias at long-term follow-up, but unable to distinguish between factors contributing independently to the scores of QoL in its eight dimensions [131-134]. The generic form facilitates comparisons and promotes understanding of QoL in different patient cohorts, but may leave important specific issues unanswered. Therefore, it was supplied with an additional questionnaire.

**Quality of life after thoracic aortic surgery – good enough?**

In the mixed patient population of study V, health-related QoL at a median of 28 months after surgery was lower than the sex- and age-adjusted normal Swedish population [131] in seven out of eight dimensions; not for bodily pain. In another five dimensions, the difference in SF-36 scores was less than 10, but for role emotional and role physical, it was 20 and 30, respectively. Obviously, overall SF-36 scores were lower in these patients. Whether these differences were of a magnitude and distribution to question the surgical treatment is speculative. In our interpretation it was positive that pain was not an issue, and that differences were more pronounced in role functioning than in eg general health and vitality. The findings of 66% expressing preserved or improved general health perception; 82% reporting preserved or improved QoL and 91% judging the operation successful were
reassuring and promoted a summarizing judgment of the postoperative health-related QoL at follow-up as acceptable.

**The impact of complications on postoperative quality of life**

We hypothesized that patients operated acutely would have worse postoperative QoL due to a higher risk of complications, but also due to their sudden transformation from “healthy” to “sick” (as in the younger, otherwise healthy patient with acute aortic dissection). At follow-up, no such differences were found. However, a larger proportion of acutely operated patients may have succumbed perioperatively or during follow-up, and their mean age was almost certainly lower than for the electively operated group.

We also hypothesized that QoL would differ in relation to aortic segment operated; specifically that it would be lower in patients operated in the descending or thoracoabdominal aorta, again due to a larger risk of perioperative complications, more extensive incision(s) and comorbidity. A pattern of lower SF-36 scores after procedures on the descending aorta was apparent, but it was not statistically significant. Scores were almost identical in patients after procedures on the ascending aorta and aortic arch, respectively, despite the risk of cerebral complications in the latter.

Finally, we hypothesized that a major perioperative complication and/or persistent severe or mild dysfunction would negatively affect SF-36 scores. Major complication did tend to lower scores of role functioning dramatically but again, due to large variations within groups, differences were not statistically significant. Severe-mild-no dysfunction groups created a homogenous pattern of increasing scores in each of the eight dimensions, but absolute differences were small and insignificant.

**Quality of life – questions posed**

The findings of study V raise several questions. Is health-related QoL after thoracic aortic operations acceptable? In our mind, yes. Does it justify surgical treatment? Overall yes, but in specific individuals adverse outcome will result and produce sometimes very poor QoL. Is QoL related to perioperative complications and permanent dysfunction? Probably yes – to an extent. Major complications can indeed be devastating, but the ability to cope and to regain QoL should not be underestimated even when severe damage has occurred. To what extent is QoL related to factors other than the thoracic aortic operation? Age is an important factor contributing to gradually decreasing SF-36 scores [131, 132]. Chronic disease may have a large impact, even if asymptomatic, as in hypertension [189].
Using quality of life in choice of treatment strategy

Whereas QoL after valve replacement [138, 141] and coronary artery surgery [135, 137, 190] had been previously reported, no similar work preceded study V in reporting QoL after thoracic aortic surgery. More recently, Immer et al present data supporting the hypothesis of worse QoL after emergency surgery [147] and data supporting the use of SACP, which compares favorably to HCA in terms of SF-36 scores at medium-term follow-up [148]. Interestingly, a 2006 study by Winnerkvist [191] find that QoL in unoperated patients with chronic type B dissection is similar to the normal population. Given the 90% 5-year survival in the same unit for this condition [192], their findings certainly adds to the impression that such patients are best managed without surgery in the absence of complications or other forcing circumstances. QoL will be used as a secondary end-point in the INSTEAD randomized trial of endovascular vs medical therapy in type B aortic dissection [193].

Final remarks and future developments

The Newtonian proverb "If I have seen further it is by standing upon the shoulders of giants" iterates as an axiom of scientific progress. In the last decades, several Scandinavian dissertations have been devoted to thoracic aortic surgery or cerebral perfusion [101, 194-198]. They reflect the progress in the field, with refined techniques in the quest of improved outcomes.

The future holds promise of further understanding and development of SACP to produce reproducibly superior results, and of cerebral monitoring as a crucial tool for guidance of SACP and for prevention of devastating neurological complications. An experimental animal model is set up to investigate the characteristics of SACP further.

Coming studies aiming to explore the underlying mechanisms of unimproved surgical mortality in type A aortic dissections the last decade are important, along with a finer delineation of the total disease burden of thoracic aortic disease. Further studies of patients in the Swedish Heart Surgery register are underway, exploring the impact of valve procedures on short- and long-term mortality, as well as short- and long-term morbidity and subsequent hospitalizations.

The advent of endovascular stent-grafts to treat thoracic aortic disease distal of the arch is only a good decade away [199], but the method has rapidly become a mainstay in therapy. Hopefully, a spectrum of disorders including traumatic injury, aneurysm, acute and chronic type B dissection as well as residual dissection after surgery and late aortic complications will be amenable to less invasive therapy if it stands the test of time. The method is already employed successfully as part of a hybrid endovascular-surgical approach in
aortic arch procedures (with so-called debranching of the arch), and it is only a matter of time before endovascular procedures become an option in the treatment of ascending aortic disease.

Aims for the future should be to reduce elective thoracic aortic operations to low-risk operations comparable to other cardiac procedures; to reduce mortality and morbidity of acute operations to a minimum; to systematically prevent cerebral complications; and to restore life expectancy and quality of life in surgical survivors by medical therapy, close and sustained follow-up and timely reinterventions performed at lowest possible risk.
Conclusions

The incidence of and operations for thoracic aortic disease in Sweden increased steadily in both sexes since 1987.

Surgical and long-term mortality improved over the last decades, overall and for thoracic aortic aneurysms, but not for aortic dissections.

Aortic dissection, acute operation, reoperation, CABG, increasing age, early period of operation, stroke and renal failure were associated with operative mortality whereas only increased age remained a statistically significant risk factor of death at long-term (> 5 years) follow-up.

Bilateral SACP entailed fewer strokes than unilateral SACP and unilateral SACP was a strong independent risk factor for stroke.

Seldinger-type direct cannulation of the right subclavian artery for CPB and SACP was feasible and safe.

Intraoperative monitoring of regional cerebral tissue oxygen saturation (rSO₂) was feasible, clinically useful, and performed well as a diagnostic instrument in prediction of perioperative stroke.

The adjusted health-related quality of life (QoL) in medium- to long-term survivors of thoracic aortic surgery was lower than in the normal population.

QoL was similar regardless of acuity and diagnosis, but tended to be worse in patients operated in the descending or thoracoabdominal aorta. The occurrence of a major perioperative complication or the presence of physical dysfunction affected QoL, but differences were not statistically significant.
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