A systematic review of the outcomes of open-heart paediatric surgery

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Executive summary

Background and objectives

This review was commissioned by the Bristol Royal Infirmary Inquiry with the aim that it would contribute to an understanding of the knowledge-base that might reasonably be expected to have been available to Bristol clinicians during 1984-1995. The review has focused on the procedures that gave rise to expressions of concern at Bristol, namely the higher risk open cardiac procedures in infants and neonates: (a) transposition of the great arteries (TGA), (b) complete atrio-ventricular septal defect (c-AVSD), (c) total anomalous pulmonary venous drainage (TAPVD), (d) truncus arteriosus and (e) the Fontan procedure. The primary objective was to identify and synthesise evidence on 30-day mortality for each procedure.

Methods

Evidence was identified by systematic literature searches using the electronic database Medline covering the period 1966-1995, which generated 1641 citations. Citations were independently selected as relevant by two reviewers and 449 full text papers were obtained, of which 165 were considered eligible for the review after detailed examination. Key data were extracted from each paper according to a protocol. Analyses were carried out by regression modelling, calculating confidence intervals to take account of clustering of patients within case series. Pooled mortality estimates were reported for each procedure and for relevant clinical sub-groups for different periods in time.

Nature of the evidence

Searches only yielded case-series, i.e. no comparative studies such as randomised trials or cohort studies were found. The number of eligible case series ranged from 58 for Fontan to 15 for truncus arteriosus, reporting data for over 2000 individuals for TGA, c-AVSD and Fontan and about 600 individuals for TAPVD and truncus arteriosus. The majority of case series were collected in the USA and about a third appeared to have been published by recognised centres of excellence.

Results

Pooled estimates of 30-day mortality were lower for the three more commonly reported procedures (TGA – 11.2%; c-AVSD – 14.7%; Fontan – 14.8%) than for the two rarer procedures (TAPVD – 24.0%; truncus arteriosus – 23.0%), although the confidence intervals for these estimates often overlapped.

Within each operation type, 30-day mortality varied for different clinical sub-groups, sometimes by a factor of two or more. These relative differences in mortality were broadly consistent with the experience of clinical experts. The review also demonstrated consistent improvements in mortality over time for all five operations.

We hypothesised that poor quality case series would tend to report lower mortality as a result of selection biases. However, the quality criteria that were assessed showed no clear association with mortality. It is unclear whether this finding arises because the criteria were inappropriate or because there was truly no association between quality and mortality.

Longer-term outcomes, such as deterioration in functional and neurological status, the need for re-intervention, late deaths attributable to operation-related factors and non-cardiac disorders, were described in some papers. However, the quality and detail of reporting of such outcomes was inconsistent across papers, making it impossible to attribute them to relevant clinical sub-groups or to generate meaningful quantitative estimates of their frequency.

Variation between case series highlighted the need for individual surgeons to monitor their practice and to contribute these data to a national database. There are well recognised methods for weighting local and national data to estimate the current risk in a local setting.

Conclusions

The pooled 30-day mortality estimates (at a particular point in time) reported in the review are likely to represent 'best achievable performance' rather than the performance to be expected in everyday practice. There was clear evidence of differences in mortality between clinical sub-groups of each operation type, which probably justifies trying to define these clinical sub-groups unambiguously in the future, as a simple measure of case-mix.

Relative to other kinds of evidence on the effectiveness of health care interventions, case series are usually regarded as contributing less strong evidence than cohort and trial designs that include an explicit control group. Consequently, reviewers have traditionally cautioned against any attempt to pool such evidence quantitatively. However, clear findings consistent with clinical opinion emerged from this review and we believe that there is a need for a methodological debate about the types of research question that systematic reviews of case series may be able to address. The quality of the source material is a key issue, in particular publication of the same data by authors in more than one publication.

The review summarises knowledge that accumulated over time. However, by analogy with other literature on systematic reviews, it is probably unrealistic to have expected practising clinicians to be aware of this knowledge.

There are serious doubts about generalising absolute estimates of mortality from case series to everyday practice. This problem highlights the need for individual surgeons to collect high quality data on their own practices, and to combine these data with national performance estimates, in order to be able to inform patients and their families about likely outcomes. Data collection should be carried out in accordance with recognised standards and definitions.

Glossary

Case-mix   A description of the severity or complexity of a disease

Case-reports   Presentation of data on a small number of non-consecutive cases of special interest that are not representative of the general study population

Case series   A series of clinical cases, usually consisting of consecutive patients, seen in one or more centres between two time points

Cohort   Any designated group of patients with some experience in common, who are followed over time

Co-morbidity   Disease(s) that co-exist(s) in a person in addition to the condition that is of primary interest or concern

Confidence interval (95%)   An estimate of mortality is based on a sample of cases. An estimate allows an inference to be made about the 'true' (but unobservable) mortality in the population from which the sample was drawn. The confidence interval is a measure of the uncertainty of the estimate, representing the range in which the true population value is likely to lie

Congenital   Describes a condition that is recognised at birth or is believed to have been present since birth. Includes all disorders present at birth that are inherited or caused by an environmental factor

Covariate   Factors that are associated with the outcome of interest, which are usually not controlled, e.g. age, and not of primary interest

Effectiveness   A measure of the extent to which a specific intervention, procedure, regimen or service does what it purports to do for a specified population

Inter-rater reliability   Consistency of observation between one reviewer and another

Intra-rater reliability   Consistency of observation of one reviewer on repeat measurement

Morbidity   The state of being diseased

Multi-centre study   A study which collects data from more than one centre

Glossary (cont.)

Odds ratio
Literally, the odds of an outcome in one group divided by the odds of the outcome in another group; hence, a measure of the relative risk of the outcome in one group compared to another

Pooled mortality estimate
A mortality estimate derived by combining data from two or more studies. Special methods have to be used to calculate the confidence interval for such an estimate, to take account of the similarities between patients within a study

Publication bias
Tendency of authors to publish articles containing positive or good findings, especially 'new' results

Randomised controlled trial
A study in which patients are randomly allocated into groups to receive or not to receive an experimental, preventative or therapeutic procedure, manoeuvre or intervention

Regression modelling
Statistical analysis which quantifies the extent to which an outcome can be explained by factors (predictors) that have been measured; e.g. in this review, the extent to which clinical sub-groups or the time of data collection explains variation in mortality

Reliability
A measure of the extent to which a measurement procedure is reproducible; reproducibility can be quantified both within (intra-observer reliability) and between (inter-observer reliability) observers

Stratification
The process of separating a sample into several subsamples according to specified criteria

Systematic review
The systematic, organised and structured evaluation of a problem, using information from a number of independent studies of the problem with the aim to integrate findings, pool the data and identify the overall trend of results

Abbreviations

All_uvh	all univentricular heart defects
c-AVSD	complete atrioventricular septal defect
COA	coarctation of aorta
DILV	double inlet left ventricle
DMVO	double mitral valve orifice
DORV	double outlet right ventricle
HLHS	hypoplastic left heart syndrome
IAA	interrupted aortic arch
IVS	intact ventricular septum
LA	language of publication
LSVC	left superior vena cava
MeSH	medical subject heading
PA	pulmonary atresia
PAB	pulmonary artery banding
PS	pulmonary stenosis
PY	publication year
RCT	randomised controlled trial
SVO	single ventricle, other
TA	tricuspid atresia
TAPVD	total anomalous pulmonary venous drainage
TB	Taussig-Bing anomaly
TCPC	total cavopulmonary connection
TGA	transposition of the great arteries
TOF	tetralogy of Fallot
VSD	ventricular septal defect

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1   Background

1   A key issue to be investigated by the Inquiry concerns the nature and outcomes of paediatric cardiac surgical services at Bristol, referred to as Issue C in the Issues List published by the Inquiry in March 1999. It was recognised that data on outcomes at Bristol needed to be interpreted by comparison with data from other centres. The Inquiry published a consultation paper outlining its approach to making use of existing data and subsequently a number of key data sources were identified, together with a phased approach to making effective and appropriate use of them. In July 1999, the Inquiry published a preliminary overview with an assessment of their strengths, weaknesses and limitations.

2   To complement work analysing existing data sources, the Bristol Inquiry commissioned a systematic review of the research evidence on the effectiveness and outcomes of paediatric cardiac surgery, with particular reference to the period 1984-1995. The review was to focus on the procedures that gave rise to expressions of concern at Bristol, namely the higher risk open cardiac procedures in infants and neonates.

3   The Inquiry commissioned this review with the aim that it would contribute to understanding of:
   (i)   the knowledge-base that might reasonably be expected to have been available to Bristol clinicians during 1984-1995 – an important area of concern for the Inquiry;
   (ii)   patient characteristics and other factors affecting surgical risk, which should therefore be taken into account when assessing an individual patient's risk;
   (iii) wider research evidence on surgical outcomes to help inform the Inquiry's assessment of the adequacy of paediatric surgical services at Bristol

4   The review had the following specific objectives:
   (i)   to identify and synthesise published evidence on 30-day mortality, the most commonly reported mortality statistic, for five higher risk open cardiac operations and defect types;

(ii)   to extract, where available, relevant information describing case-mix and to investigate associations between patient characteristics and 30-day mortality;

(iii)   to test the robustness of the synthesised evidence by investigating associations between, on the one hand, study design and reporting quality and, on the other, 30-day mortality;

(iv)   to identify longer-term outcomes reported in the published literature;

(v)   to identify patient characteristics that require to be taken into account when determining and then communicating surgical risk;

(vi)   to interpret the research evidence in relation to the aims of the Inquiry, including the extent to which evidence from the literature would be expected to apply to paediatric cardiac surgical services at Bristol.

2. Methods

2.1 Search Strategy

5 Systematic literature searches were carried out using the National Library of Medicine's electronic database Medline on the Silverplatter software interface, using databases from 1966-1995. 1966 represents the first year when Medline was published electronically. Pre-1966 references cited in later publications would have been eligible for inclusion but none were identified. It was not feasible to hand-search journals for publications prior to 1966.

6 Initial searches were run using both keywords and the thesaurus facility to identify Medline Subject Headings (MeSH), where available. We limited the search to the Medline database as it includes citations from all important cardiothoracic surgery and cardiology journals. No papers identified through cross-referencing were in non-Medline journals. A list of the main journals containing the papers in this review is shown in Appendix A. Appropriate synonyms and acronyms were included in the searches. Where reading of papers revealed the use of alternative terminology, search strategies were modified to include relevant additional keywords (e.g. the term endo-cardial cushion defect is also used to describe an atrioventricular septal defect). For the Fontan procedure, we included the terms 'Total Cavopulmonary Connection/Anastomosis' in our Medline search to reflect recent developments in operative techniques. Preliminary searches on the five operation types identified a total of 6831 references (Table 1).

7 The number of citations was first limited to all papers with a MeSH heading of "Infant" or "Infant-Newborn", to narrow the search to papers describing procedures on children under the age of 2 years. For the Fontan procedure we extended the search to "Child" as well as "Infant" or "Infant-Newborn". "Child" in Medline refers to all children aged 2-12 years of age.

8 It was decided to limit further the number of citations using the MeSH heading "Heart-Defects-Congenital" with 'surgery' as a subheading. This approach proved more appropriate than using "Cardiac-Surgical-Procedures" or "Thoracic-Surgery',

due to inconsistent and inappropriate indexing of citations with these latter MeSH headings. Finally, search strategies were limited to those citations published in English. For the arterial switch operation for TGA, citations were limited to those published after 1974 since the first arterial switch operation was carried out in 1975. Placing these limits on the search strategy reduced the number of citations to 1641 (Table 1). A small number of citations were identified through cross-referencing (Table 2). Search strategies for each operation type can be seen in Appendices B-F.

9   Each abstract, where available, was read and independently assessed by two observers and its relevance to the review determined. All of these were read to determine their eligibility for inclusion.

2.2   Selection of eligible papers

10   Papers were categorised by primary defect or operation type. If the search identified a paper in which the keyword pertained to an associated defect, and not the primary defect or operation type, the paper was re-classified appropriately. As not all abstracts were available on the electronic database, or because the abstracts were misleading, a number of papers was found on reading to be inappropriate for the review. Publications describing case-reports, case series of less than 10 patients and those where 30-day post-operative mortality was not reported were also excluded from the review. It was felt that results obtained from papers describing case series of fewer than 10 patients may not be generalisable and may be due to selection bias as a result of inclusion of non-consecutive cases. Case series with a total sample size of 10 or more patients where the sample was sub-divided for reporting purposes into groups by some relevant characteristic, e.g. comorbidity, were included. The number of papers excluded can be seen in Table 2 and in appendices B-F. All papers included in our analyses are listed in Appendix H.

Table 1: Number of citations identified on the Medline database (1966-1995)

Operation type	Number of citations identified	Number of citations after limiting [a]	Number of citations selected
Arterial switch operation for transposition of great arteries	3634 [b]	879	100
Correction of atrioventricular septal defects	630	134	104
Correction of total anomalous pulmonary venous drainage	372	63	45
Correction of truncus arteriosus	726	151	52
Fontan procedure for univentricular heart defects	1469 [c]	416	135
Total	**6831**	**1641**	**436**

[a] Number of citations limited by: (a) "Infant"/ all subheadings, (b) "Heart-defects-Congenital"/surgery, (c) Language = "English"

[b] Number of citations also limited by: Publication year $\geq$ 1975

[c] Number of citations limited by: (a) "Infant" or "Child"/ all subheadings, (b) "Heart-defects-Congenital"/surgery, (c) Language = "English"

Table 2: Number of papers included in and excluded from this review

Operation type	TGA	AVSD	TAPVD	Truncus Arteriosus	Fontan	Total
Citations selected	100	104	45	52	135	436
Citations found by cross-referencing	6	0	5	2	0	13
Irrelevant papers	44	26	14	9	33	126
Papers publishing duplicated data	13	10	3	2	24	52
Case reports	5	13	9	15	0	42
Unavailable	5	0	1	0	2	8
Case series <10	5	16	4	13	18	56
Eligible for review	34	39	19	15	58	165

Table 3: Inter-rater agreement for coding of quality variables

Question	Agreement %	Expected agreement %	Kappa score
1	88	81.9	0.34
2 $^\alpha$			
3	80	57.9	0.53
4	100	68.0	1.00
5	84	56.2	0.64
6	96	48.0	0.92
7	96	75.8	0.83

α Kappa values cannot be calculated because all reviewers assigned the same rating (yes) to all papers

2.3   Data extraction

11   A data extraction form was devised and piloted on 10 papers to identify appropriate and inappropriate use of original variables. A copy of the final form can be seen in Appendix G. Data on mean weight and age of infants were extracted for each case series, where available. Where only a range was given, the midpoint was used and ages were converted into consistent units. Due to the complexity of the papers, each operation type was read by the same reviewer who could therefore develop sufficient expertise to classify papers accurately and consistently. All queries were resolved by team discussions. The data were entered on a spreadsheet (Excel) and imported into Stata (a statistical software package) for analysis. A number of major centres presented analyses of sub-groups of consecutive patients seen at their centre; data from one group of patients could therefore be published more than once. This was seen primarily in papers describing the Fontan procedure. Papers presenting duplicated data were excluded where possible (see Limitations of Study).

2.4   Quality assessment of studies

12   Studies were assessed against seven 'quality' variables to provide a guide to the extent to which the findings of each study could be relied upon and to highlight any methodological flaws. These were:

- case series collected in more than one centre, i.e. multi-centre study
- aims of case series clearly stated
- case definition clearly reported
- explicit statement that patients were recruited consecutively
- reporting of confidence intervals, or other estimate of random variability
- reporting of mortality stratified by comorbidity
- definition of 30-day mortality reported
- reference to patient selection criteria in Fontan case series e.g. the Choussat criteria.

Quality assessment criteria for case series are not well established but similar criteria have been collected in other systematic reviews of case series [1].

13   The general readability and quality of papers was found to vary greatly and, for the most part, to improve over time. Particular attention was paid to intra-observer

reliability; the variables were checked and re-assigned if reviewers were unsure of their consistency in scoring quality during the course of the review.

2.5   Case-mix variables

14   The eligible papers revealed that each cardiac defect or operation type could take a variety of different forms. Transposition of the great arteries, for example, presents with an intact ventricular septum or with a ventricular septal defect.

15   30-day post-operative mortality estimates had, therefore, to be stratified by sub-types. This was possible for most papers, but where the mortality estimate was only provided for the case series as a whole, an 'unstratified group' was described. Data from a single publication could therefore generate more than one line in the database, depending on the types of patients in the case series. Similar methods of stratification were applied to all operation types. Strata for each operation type are described in section 3. Where papers described a single sub-type, e.g. a series of patients with TGA with an intact ventricular septum, in which patients were stratified by age group, this was reflected in the database.

2.6   Inter-observer reliability

16   A reliability study was carried out to assess the degree of inter-observer variability. Five papers for each of the five operation/defect types were chosen at random and the quality scores independently assessed by a different member of the review team. The Kappa statistic, a non-parametric measure of inter-rater agreement, was calculated for each of the seven quality variables (Table 3). Measure of agreement is scaled from zero to one, zero when the amount of agreement is what would be expected by chance and one suggesting perfect agreement. Kappa values appear inconsistent with 'agreement' in some cases because of the uniformity of the responses across evaluations for some criteria. When responses are relatively uniform, it is very difficult to obtain a high Kappa score because 'expected' agreement is also high.

2.7   Methods of analysis

17   Analyses were carried out by regression modelling using Stata v.6 statistical software, using a 'robust' method to calculate confidence intervals; this method takes account of clustering of patients within case series.

18   The results for each operation type are displayed graphically, showing each estimate for 30-day mortality with a 95% confidence interval plotted against the mid-point date for the period of data collection for the case series. Additional graphs are included for case-mix subgroups.

19   In addition to estimating 30-day mortality for relevant clinical sub-groups, we also explored the extent to which other attributes of case series (covariates) were associated with mortality, namely (a) the time when the case series was collected, (b) the average age of the patients recruited and (c) the quality criteria assessed by reviewers. We investigated the time of data collection by calculating a 'mid-point date' for each case series from the reported date when data collection started and duration of the study.

20   Regression modelling was carried out in stages. First, an overall pooled estimate of mortality, and a corresponding confidence interval, were derived for all case series for each operation type. Next, clinical sub-groups were included, followed by mid-point date and age and, finally, quality criteria. Mid-point date and age were modelled in appropriate groups, e.g. '1975 to 1979' or '3 to 12 months of age', rather than as continuous variables. This approach allowed us to include case series where these covariates were not reported in a separate 'missing' group. We have therefore made no attempt to superimpose linear trends with time on the graphs of mortality estimates for case series and have instead tabulated mortality estimates for different clinical sub-groups and time periods.

3. Results

3.1 The nature of the evidence

3.1.1 Transposition of the great arteries

21 Transposition of the great arteries (TGA) is the second most common form of cyanotic (bluish discolouration of skin resulting from inadequate amount of oxygen in the blood) congenital heart disease [2]. In these patients, the great arteries are 'transposed', the right ventricle giving rise to the aorta, thus carrying deoxygenated blood to the systemic circulation, and the left ventricle giving rise to the pulmonary artery, carrying oxygenated blood to the lungs.

22 Infants with TGA are severely cyanosed at birth and most will die if left untreated. Short-term survival requires some mixing between the pulmonary and systemic circulations since patients with inadequate mixing die of cyanosis. For some patients, sufficient mixing can occur naturally if there is a large enough ASD, VSD or PDA, but most will require a balloon atrial septostomy. Later surgical repair is still required. If an arterial switch is to be undertaken, patients with a TGA and intact ventricular septum must be operated on in the first few weeks of life, before pulmonary resistance falls to a post-natal level [3]. Those with an associated VSD are operated on within the first few months of life.

23 Early attempts to correct TGA physiologically involved redirecting blood flow at the atrial level, utilising the Mustard [4] and Senning [5] operative procedures, but the left ventricle still gave rise to the pulmonary artery and the right ventricle to the aorta. Although short-term survival rates achieved by these operation types were good, long-term complications such as tricuspid regurgitation, right ventricular dysfunction and serious arrhythmias were frequently reported [6].

24 Jatene performed the first anatomical correction of TGA in 1975, by switching the great arteries and separately transferring the coronary arteries to the neo-aorta. However, many centres were slow to adopt this new approach because of the high mortality rates, particularly in comparison to the low risk associated with the Mustard and Senning procedures. Coronary artery transfer was also a highly complex

procedure and so alternative techniques were developed to avoid moving the coronary arteries [7,8]. The most important modification of the original Jatene switch procedure was probably the Lecompte manoeuvre [9]. Arterial switch retained its appeal because of its theoretical advantage with the left ventricle supporting the systemic circulation.

25 Using the search strategy described in Appendix B, a total of 34 eligible case series of TGA were identified, which reported data for 4051 individuals. The characteristics of these case series are summarised below in Table 4.

Table 4: Characteristics of 34 case series of TGA

Characteristic	median	range	frequency	%
Sample size	65	10 to 513		
30-day mortality	9%	0 to 60%		
Case series start date	1984	1975 to 1992		
Case series publication date	1991	1982 to 1995		
Duration of case series (months)	56	10 to 240		
Time lag to publication (years)	1	0 to 3		
'Average' age (days) [a]	13	3 to 1030		
Case series (cases) by country:				
UK			3 (198)	9 (5)
USA and Canada			13 (1770)	38 (44)
Europe other than UK			11 (1297)	32 (32)
All other countries			7 (773)	21 (19)
Quality criteria:				
Multi-centre studies			6	18
Clear statement of aims			34	100
Case definition reported			33	97
Consecutive patients			30	88
Confidence intervals reported			10	29
Stratified by comorbidity			21	62
30-day mortality defined			26	76
Satisfied > 4 quality criteria			22	65

[a]   Average age: mean or any other measure of central tendency when mean not available, e.g. median, midpoint of range, etc. Available for 24 studies only.

3.1.2 Atrioventricular septal defects

26   Atrioventricular septal defects (AVSDs) account for 4.2% of all congenital cardiac abnormalities [10]. In its complete form, AVSD is characterised by deficiency of the atrial and ventricular septa and both mitral and tricuspid valves. AVSD can also be partial but it is the complete form that is the subject of the review. The size of defects, the pulmonary vascular resistance and the degree of AV valve incompetence determine the extent of haemodynamic abnormality and the age of clinical presentation, which is normally in early infancy. The natural history of unoperated

AVSD is generally poor [11], although most patients do survive childhood, pulmonary vascular disease will develop if an AVSD is uncorrected and most will die in their 20s or 30s [12].

27   In the late 1970s and early 1980s most patients with a complete AVSD were operated on before two years of age [13]. Ever since the operation was successfully performed by Lillehei et al in 1954 [14], there has been much debate over the merits of palliative treatments in the short term, e.g. pulmonary artery banding, versus a single-stage operative correction [15]. Over the last 20 years, the tendency has been to take the latter course because, in addition to improvements in surgical technique and a subsequent reduction in peri-operative mortality, pulmonary banding has provided unpredictable results [16].

28   Congenital heart disease is a well-recognised clinical feature in children with Down's syndrome and AVSD is the commonest cardiac lesion in this population. Few studies however, have suggested Down's syndrome as a risk factor for peri-operative death [17,18].

29   A total of 39 eligible case series of c-AVSD were identified which reported data for 2420 individuals. The characteristics of these case series are summarised in Table 5.

Table 5: Characteristics of 39 case series of c-AVSD

Characteristic	median	range	frequency	%
Sample size	40	4 to 301		
30-day mortality	10%	0 to 64%		
Case series start date [a]	1975	1960 to 1989		
Case series publication date	1989	1968 to 1995		
Duration of case series (months) [a]	120	36 to 252		
Time lag to publication (years) [a]	1	0 to 7.8		
'Average' age (months) [b]	41	1.4 to 229		
Case series (cases) by country:				
UK			2 (105)	5 (4)
USA and Canada			23 (1779)	59 (73)
Europe other than UK			7 (411)	18 (17)
All other countries			7 (155)	18 (6)
Quality criteria:				
Multi-centre studies			3	8
Clear statement of aims			38	97
Case definition reported			39	100
Consecutive patients			24	62
Confidence intervals reported			7	18
Stratified by comorbidity			19	49
30-day mortality defined			37	92
Satisfied > 4 quality criteria			16	41

[a] Case series start date, duration and time lag to publication were available for 38 studies only.

[b] Average age: mean or any other measure of central tendency when mean not available, e.g. median, midpoint of range, etc. Available for 36 studies only.

3.1.3 Total Anomalous Pulmonary Venous Drainage

30   Total Anomalous Pulmonary Venous Drainage (TAPVD) comprises 1.5% of all congenital cardiac abnormalities [19]. In patients with this condition, the pulmonary veins do not drain to the left atrium but instead join a systemic vein so that the blood reaches the right atrium; for some the connection with the systemic vein is also obstructed. The first complete repair of TAPVD was carried out in 1956 [20]. The majority of patients present in the first few weeks of life suffering from hypoxia, heart failure and respiratory distress [21-24]. Corrective surgery is the only option for TAPVD patients, since 80% will die within a year if left untreated [25].

31   A total of 19 eligible case series of TAPVD were identified which reported data for 651 individuals. The characteristics of these case series are summarised in Table 6.

Table 6: Characteristics of 19 case series of TAPVD

Characteristic	median	range	frequency	%
Sample size	20	7 to 83		
30-day mortality	25%	0 to 65%		
Case series start date [a]	1971	1955 to 1979		
Case series publication date	1985	1966 to 1994		
Duration of case series (months) [a]	108	52 to 216		
Time lag to publication (years) [a]	2	0 to 7.4		
'Average' age (days) [b]	65	15 to 464		
Case series (cases) by country:				
UK			5 (260)	26 (40)
USA			8 (230)	42 (35)
Europe other than UK			4 (100)	21 (15)
All other countries			2 (61)	11 (9)
Quality criteria:				
Multi-centre studies			1	5
Clear statement of aims			19	100
Case definition reported			19	100
Consecutive patients			17	89
Confidence intervals reported			1	5
Stratified by comorbidity			16	84
30-day mortality defined			17	89
Satisfied > 4 quality criteria			6	32

[a] Case series start date, duration and time lag to publication were available for 17 studies only.

[b] Average age: mean or any other measure of central tendency when mean not available, e.g. median, midpoint of range, etc. Available for 13 studies only.

3.1.4 Truncus Arteriosus

32   Truncus arteriosus is an abnormality in which a single arterial trunk gives rise to the systemic and pulmonary circulations. The incidence of truncus arteriosus is approximately 4 per 100,000 live births [26]. Surgical treatment for this operation is crucial since 70% of patients die within three months of life if left untreated [27]. The first successful surgical repair of truncus arteriosus was carried out in 1968 [28]. Early repair of truncus arteriosus has better results and it is now standard procedure to operate, where possible, on infants less than 6 weeks of age [29]. The surgical procedure adopted for truncus arteriosus depends on the pulmonary artery anatomy [30]. According to Collett and Edwards's classification [31], the site at which the pulmonary arteries arise from the common arterial trunk determines the type of truncus arteriosus. The variations of truncal anatomy are not thought to influence surgical risk.

33   A total of 15 case series of Truncus Arteriosus were identified which reported data for 579 individuals. The characteristics of these case series are summarised in Table 7.

Table 7: Characteristics of 15 case series of Truncus Arteriosus

Characteristic	median	range	frequency	%
Sample size	23	12 to 100		
30-day mortality	21%	11 to 62%		
Case series start date [a]	1975	1965 to 1987		
Case series publication date	1985	1974 to 1994		
Duration of case series (months) [a]	72	38 to 204		
Time lag to publication (years) [a]	1.4	0 to 5.8		
'Average' age (months) [b]	4.2	1 to 156		
Case series (cases) by country:				
UK			3 (45)	19% (8%)
USA			9 (475)	63% (82%)
Europe other than UK			2 (36)	13% (6%)
All other countries			1 (23)	6% (4%)
Quality criteria:				
Multi-centre studies			0	0%
Clear statement of aims			15	100%
Case definition reported			15	100%
Consecutive patients			14	93%
Confidence intervals reported			2	13%
Stratified by comorbidity			9	60%
30-day mortality defined			13	87%
Satisfied > 4 quality criteria			8	53%

[a]   Case series start date, duration and time lag to publication were available for 15 studies only.

[b]   Average age: mean or any other measure of central tendency when mean not available, e.g. median, midpoint of range, etc. Available for 14 studies only.

3.1.5   The Fontan procedure

34   The Fontan procedure is a palliative operation for children with congenital heart defects which preclude a bi-ventricular circulation and, irrespective of the primary defect, is ultimately performed to redirect systemic venous return directly to the pulmonary arteries. Fontan and Baudet first described a procedure to bypass the right heart as surgical treatment for tricuspid atresia (TA), in 1968 [32]. TA is the most common form of univentricular heart in a range of complex congenital disorders whose natural history is poor; 50% of patients with tricuspid atresia die before reaching 6 months of age if untreated [33].

35   Since it was first applied to TA, the Fontan principle of right heart bypass has become the definitive palliation for an increasing range of heart defects with only one functional ventricle, including hypoplastic left heart (HLH), and heterotaxy syndromes [34,35].

36   In the Fontan procedure, physiology is more predictive of outcome and Choussat defined 10 criteria that should be fulfilled by a patient before being selected for a Fontan operation [36]. However, it has since been argued that one or even two criteria may not be met without jeopardising the result [37,38]. A favourable outcome of a Fontan procedure requires a favourable profile of pulmonary vascular physiology, ventricular function and rhythm stability. By separating the pulmonary and systemic circulations, a successful Fontan reduces volume overload in the ventricle and relieves arterial hypoxemia.

37   Most patients having a Fontan procedure would have had previous operations. For many, palliation in early infancy will have been required to achieve a stable and durable physiology that ultimately lends itself to a successful outcome for a future complete Fontan-type of reconstruction. Such earlier procedures may include: systemic pulmonary shunts, pulmonary artery bands, Glenn procedures, Damus-Kaye-Stansel operations or Norwood procedures. A more recent variation of the Fontan operation (atriopulmonary connection) is total cavopulmonary connection (TCPC) which was developed in the 1980s [39] in an attempt to improve blood flow to the pulmonary arteries. A fenestration in the Fontan circuit allows some mixing of

oxygenated and de-oxygenated blood [40], and this may reduce post-operative effusions and contribute to a better post-operative course.

38   A total of 58 case series of Fontan were identified which reported data for 4409 individuals. The characteristics of these case series are summarised in Table 8.

Table 8: Characteristics of 58 case series of Fontan

Characteristic	median	range	frequency	%
Sample size	31	8 to 702		
30-day mortality	14%	0 to 100%		
Case series start date [a]	1980	1953 to 1990		
Case series publication date	1992	1980 to 1995		
Duration of case series (months) [a]	89	12 to 336		
Time lag to publication (years) [a]	1	0 to 5.8		
'Average' age (months) [b]	84	12 to 221		
Case series (cases) by country:				
UK			3 (91)	5 (2)
USA			31 (3050)	53 (69)
Europe other than UK			14 (839)	24 (19)
All other countries			10 (429)	17 (10)
Quality criteria:				
Multi-centre studies			1	2
Clear statement of aims			58	100
Case definition reported			55	95
Consecutive patients			47	81
Confidence intervals reported			10	17
Stratified by comorbidity			35	60
30-day mortality defined			50	86
Use of patient selection criteria			22	38
Satisfied > 4 quality criteria			36	62

[a]   Case series start dates were available for 57 studies only, and duration and time lag to publication were available for 56 studies only.

[b]   Average age: mean or any other measure of central tendency when mean not available, e.g. median, midpoint of range, etc. Available for 43 studies only.

3.2 Stratification by case-mix

39 Transposition of the great arteries

In order to present mortality data in a more meaningful way, we attempted to describe sub-groups of patients by associated cardiac defects, which may confer different operative mortality risks. Patients with TGA are commonly categorised according to the presence of the following associated anomalies:

- with intact ventricular septum (IVS)
- with ventricular septal defect (VSD)
- with Taussig-Bing anomaly or double-outlet right ventricle with sub-pulmonary ventricular septal defect (TB)

The term 'unstratified' was used when mortality is not stratified by sub-type.

40 Atrioventricular septal defects

For the purposes of this review, we stratified AVSDs by complexity. 'Complex' AVSDs are defined as those with tetralogy of Fallot, double-outlet right ventricle or pulmonary stenosis. Ideally, AVSD patients with these abnormalities should be considered separately but most case series did not stratify mortality by associated defects and were considered as an 'unstratified' group. All other anomalies mentioned in the papers, including persistent ductus arteriosus and atrial septal defects, are classed as 'simple'.

41 Total anomalous pulmonary venous drainage

This defect is usually described by the point of drainage or anatomical position. TAPVD is sometimes a component of more complex congenital heart disease such, as heterotaxy, but this review excludes such patients. TAPVD is described as:

- Supracardiac – draining to left or right superior vena cava
- Cardiac – draining to coronary sinus or right atrium directly
- Infracardiac/infradiaphragmatic – drainage to portal vein or inferior vena cava
- Mixed – drainage to a combination of the above.

42   Truncus Arteriosus

As with AVSDs, we stratified by complexity. Those with an additional interrupted aortic arch or severe truncal valve anomalies, were considered 'complex' cases and all other anomalies were classified as 'simple'.

43   The Fontan procedure

The Fontan operation is a palliative procedure for children with congenital heart defects, which preclude a bi-ventricular repair. Virtually all univentricular heart patients with a surgical treatment plan will have a series of operations with the final one, which separates systemic and pulmonary circulation, known as the 'Fontan' procedure. We included all papers that described a population of patients having undergone a Fontan operation, atriopulmonary connection or, as is the case more recently, TCPC. We thus excluded all earlier palliative procedures dealing with pulmonary blood flow, including all shunting and banding. Where possible, we present data by defect:

- Tricuspid atresia
- Hypoplastic left heart
- Pulmonary atresia
- Single ventricle (functional), other, including:
    - univentricular heart
    - double outlet right ventricle
    - double inlet left ventricle
    - heterotaxy
- 'All univentricular hearts' includes data for case series, which do not present mortality by subgroup.

Diagrammatic representations of a normal heart and each of the defects presented can be seen in Appendix I.

3.3 Estimates of 30-day mortality

3.3.1 Transposition of great arteries (TGA)

44 Individual 30-day mortality estimates and 95% confidence intervals by calendar time are displayed in Figure 1. Crude 30-day mortality pooled across all 34 case series was 11.2% (95% CI 8.9% to 14.1%).

Figure 1: 30-day mortality estimates and 95% confidence intervals for TGA case series (n=34).
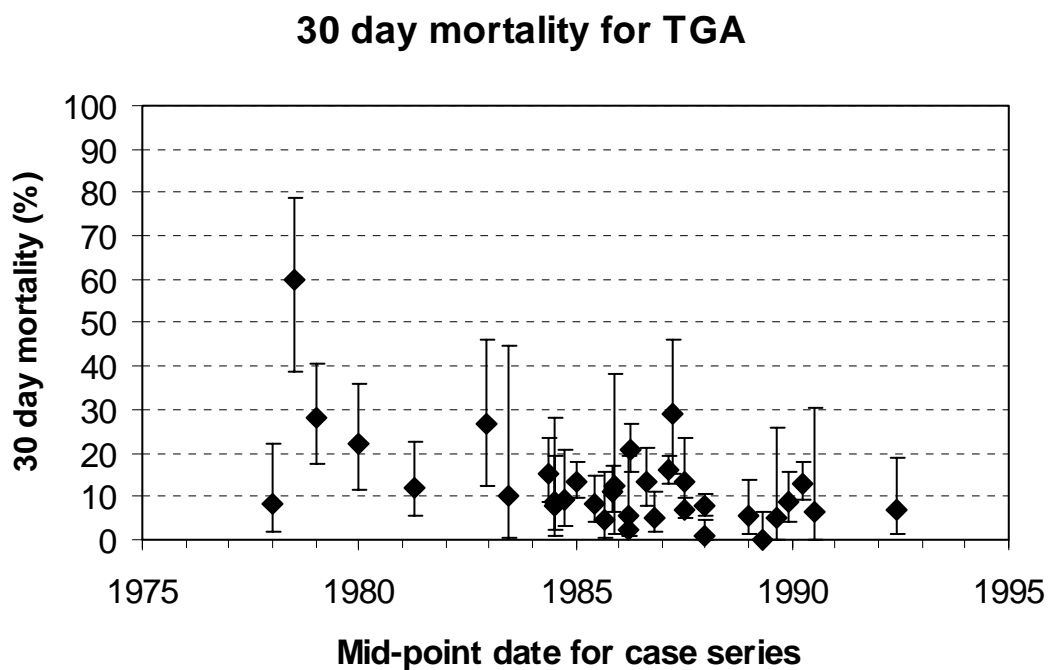
45 The majority of studies reported mortality separately for groups of patients with different additional congenital anomalies. Table 9 shows the numbers of case series and patients included in these series, 30-day mortality estimates and 95% CIs pooled across all available case series for each sub-group separately. Case series in which data were not stratified by additional defects, or where mortality was reported for an unstratified group of patients in addition to defined sub-groups, were included in the 'unstratified' sub-group. Individual 30-day mortality estimates for each case series for each sub-group and 95% confidence intervals by calendar time are displayed in Figure 1. Note that the 30-day mortality estimates presented in Figure 1 do not take

account of other differences between case series, e.g. with respect to mid-point date or the average age of patients.

Table 9: Case series of TGA reporting mortality separately for sub-groups with different combinations of congenital defects

Defect sub-group	n (studies)	n (cases)	30-day mortality (%)	95% CI
TGA with IVS (pooled over time)	**22**	**1476**	**7.7**	**5.7 to 10.3**
pre-1980	2	36	20.8	9.8 to 38.7
1980 to 1984	7	264	5.8	2.5 to 12.7
1985 to 1989	11	1001	7.6	5.7 to 10.1
1990 to 1995	2	175	7.8	5.1 to 11.8
TGA with VSD (pooled over time)	**17**	**749**	**14.4**	**10.6 to 19.3**
pre-1980	1	21	35.4	17.1 to 58.8
1980 to 1984	7	228	11.3	5.2 to 22.8
1985 to 1989	7	148	14.7	9.6 to 21.9
1990 to 1995	2	352	15.0	12.5 to 18.0
TGA with DORV (pooled over time)	**8**	**84**	**10.7**	**6.4 to 17.4**
pre-1980 [a]	0	0	-	-
1980 to 1984	4	42	9.3	4.5 to 18.3
1985 to 1989	4	42	12.0	6.1 to 22.6
1990 to 1995 [a]	0	0	-	-
Unstratified defects (pooled over time): [b]	**13**	**1729**	**12.9**	**9.2 to 17.9**
pre-1980	2	69	30.5	15.5 to 51.2
1980 to 1984	0	0	-	-
1985 to 1989	9	1601	12.2	8.4 to 17.2
1990 to 1995 [a]	2	59	12.4	7.4 to 20.0

[a] Estimates and 95% CIs not available because no case series reported data for these strata.
[b] Ten case series only reported data for a group of patients with 'unstratified' additional anomalies. A further three case series reported data for a group of patients with 'unstratified' defects in addition to data for groups of patients in at least one of the other three sub-groups.

46   The risk for TGA patients with a ventricular septal defect (VSD), a double-outlet right ventricle (DORV), or 'unstratified' defects can be contrasted with the risk for patients with an intact ventricular septum (IVS). There was no statistically significant

difference in mortality risk between IVS patients and DORV patients (odds ratio = 1.45, 95% CI 0.74 to 2.85). However, TGA patients with VSD were estimated to have a mortality risk about twice that for patients with IVS (odds ratio = 2.03, 95% CI 1.48 to 2.79). Patients in the 'unstratified' stratum had a mortality similar to the patients with VSD (odds ratio = 1.79, 95% CI 1.09 to 2.92).

Figure 2: 30-day mortality for TGA case series by anatomical sub-groups

(a) TGA with IVS
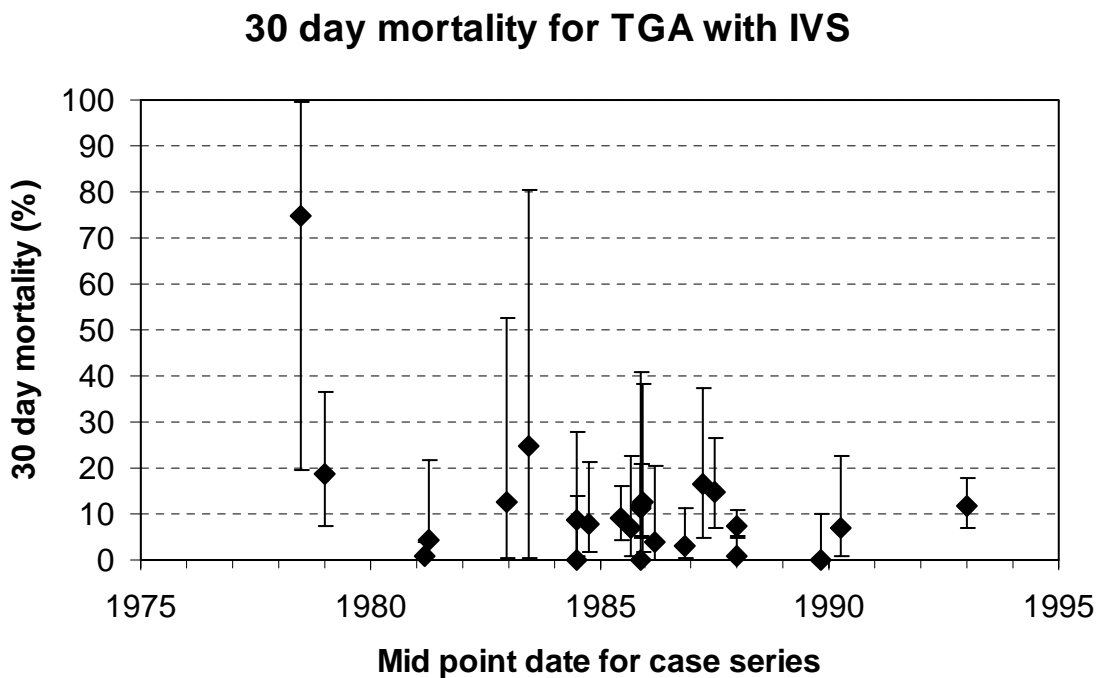
(b) TGA with VSD
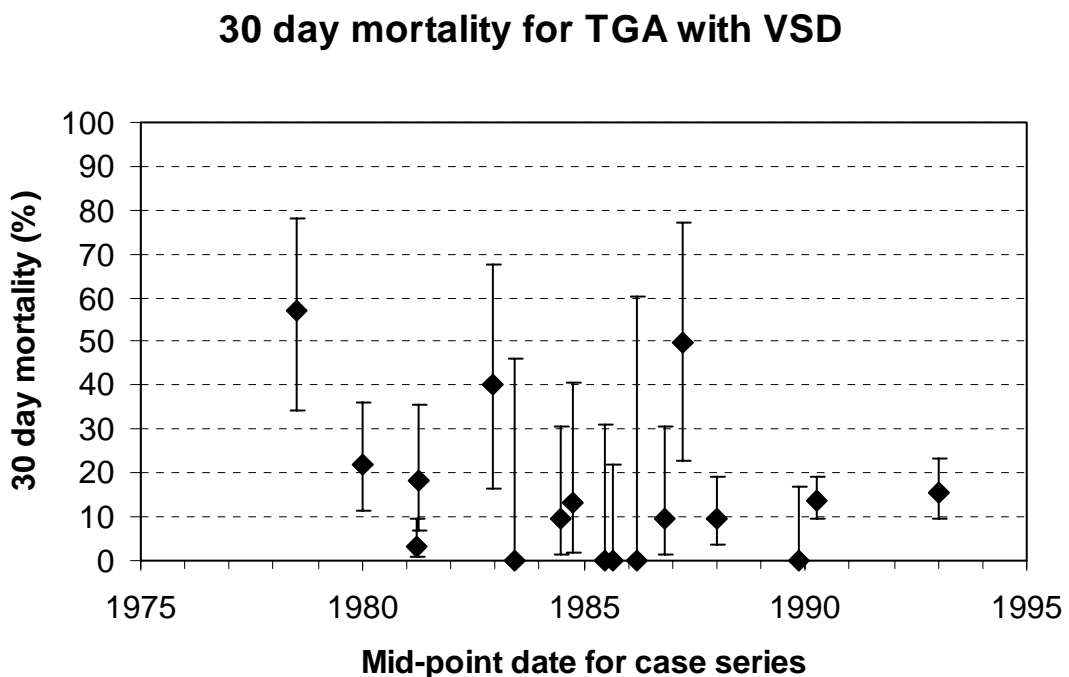
Figure 2 (cont.)

(c) TGA with DORV

30 day mortality for TGA with DORV

(d) TGA - unstratified defects
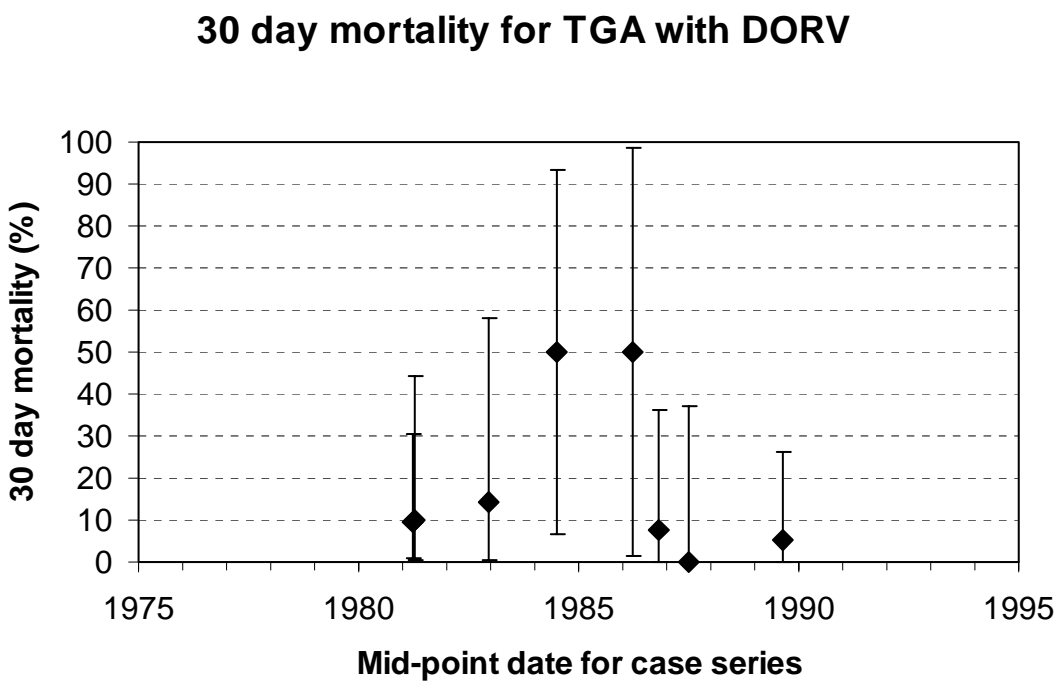
30 day mortality for TGA - unstratified defects
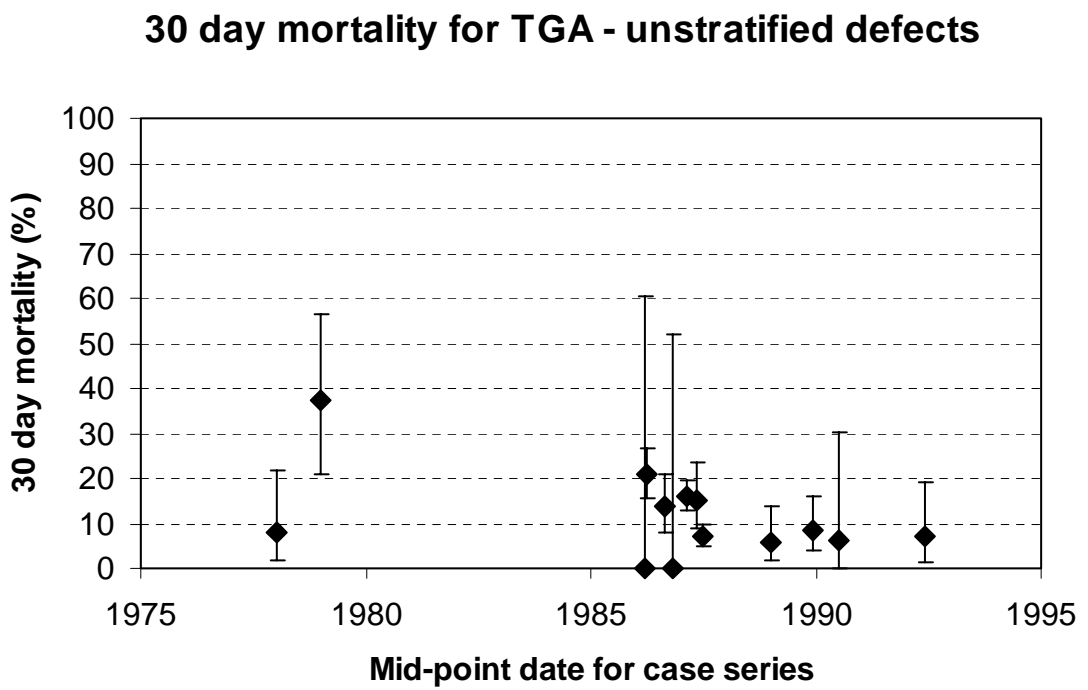
47   Changes in 30-day mortality with calendar time were investigated by classifying the mid-point dates for case series into four groups, pre-1980, 1980 to 1984, 1985 to 1989, and 1990 to 1995. After stratifying by congenital defect sub-group, 30-day mortality decreased steadily with calendar time to about one third of the risk estimated for the pre-1980 period (see Table 10); mortality estimates by defect sub-group and mid-point date are reported in Table 9.

Table 10: 30-day mortality by mid-point date for TGA case series, after taking account of sub-groups with different combinations of congenital defects

Anatomical variant	n (studies)	n (cases)	odds ratio	95% CI
Pre-1980	3	126	1.00	
1980 to 1984	8	534	0.23	0.07 to 0.79
1985 to 1989	19	2796	0.31	0.13 to 0.77
1990 to 1995	4	586	0.32	0.12 to 0.84

48   Changes in 30-day mortality with age at operation were investigated by classifying the average ages for case series into four groups, 0-10 days, 11-30-days, >30-days, and 'average age not reported'. After stratifying by anatomical defect and mid-point date, 30-day mortality in the 11-30-day group was about half that estimated for the 0-10 day group (odds ratio = 0.47, 95% CI 0.31 to 0.71); 30-day mortality in the >30-day and age unknown groups were similar to that for the 0-10 day group (>30-days: odds ratio = 0.88, 95% CI 0.47 to 1.64; age not reported: odds ratio = 0.74, 95% CI 0.42 to 1.29) Including age at operation in the analysis did not change the findings for defect sub-groups in any substantive way.

49   Three factors (multi-centre studies, the explicit statement that patients were recruited consecutively, and stratification by associated defect) were independently associated with a one and a half to two-fold increase in 30-day mortality. After including these quality criteria with mid-point date and age group, age at operation was no longer associated with 30-day mortality.

3.3.2 Complete Atrio-Ventricular Septal Defects (c-AVSD)

50   Individual 30-day mortality estimates and 95% confidence intervals by calendar time are displayed in Figure 3. Crude 30-day mortality pooled across all case series was 14.7% (95% CI 10.7% to 19.9%).

Figure 3: 30-day mortality estimates and 95% confidence intervals for c-AVSD case series (n=39). One case series, which did not report start dates or duration, is not shown.

30 day mortality for c-AVSD
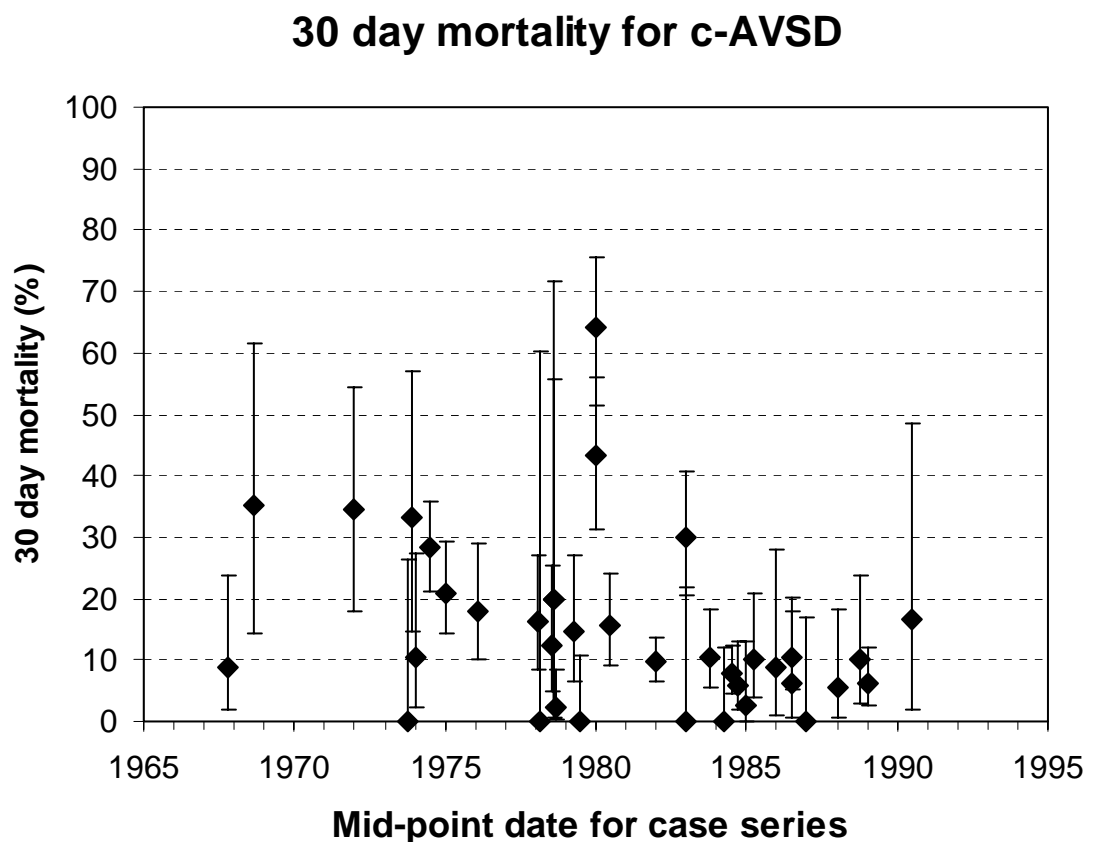
51   The majority of case series reported mortality in sufficient detail to allow data to be extracted separately for simple and complex sub-groups (see 3.2 for definitions of defects included in simple and complex categories); where this was not possible, data for case series were classified in the 'unstratified' complexity sub-group. Table 11 shows the numbers of case series and patients included in these series, the 30-day mortality estimates and 95% CIs pooled across all available case series for each sub-group separately. Individual 30-day mortality estimates for each case series in each

sub-group and 95% confidence intervals by calendar time are displayed in Figure 4. Note that the 30-day mortality estimates shown in Figure 4 do not take account of other differences between case series, e.g. with respect to mid-point date or the age of the patients.

52   The risk for patients with complex or unstratified defects can be contrasted with that for patients with simple defects. Patients with complex defects were estimated to have a mortality risk approximately double that for patients with simple defects (odds ratio = 2.51, 95% CI 1.08 to 5.87). Patients in the 'unstratified' stratum appeared to have a risk similar to patients with simple defects.

53   Changes in 30-day mortality with calendar time were investigated by classifying the mid-point dates for case series into five groups, pre-1975, 1975 to 1979, 1980 to 1984, 1985 onwards, and ''mid-point date not calculable''. After stratifying by anatomical defect, 30-day mortality between 1975 and 1984 was similar to the pre-1975 level (1975-1979:odds ratio = 0.76, 95% CI 0.35 to 1.66; 1980-1984: odds ratio = 0.87, 95% CI 0.38-2.00). However, there was a marked decrease in mortality from 1985 onwards, to about one third of the pre-1975 level (odds ratio = 0.36, 95% CI 0.19 to 0.69). The case series (unstratified complexity defects) for which a mid-point date was not calculable had mortality similar to the period from 1985 onwards. Estimates of 30-day mortality by mid-point date for each complexity group are included in Table 11.

Table 11: Case series of c-AVSD reporting mortality separately for different complexity of defects and for different mid-point dates

Complexity of defect / mid-point date	n (studies)	n (cases)	30-day mortality (%)	95% CI
Simple (pooled over time)	**21**	**1250**	**16.2**	**10.2 to 24.8**
pre-1975	4	168	20.1	13.0 to 29.9
1975 to 1979	7	202	16.1	8.9 to 27.4
1980 to 1984	6	624	18.0	9.2 to 32.3
1985 onwards	4	226	8.4	5.4 to 13.0
'mid-point date not calculable'	0	0	-	-
Complex (pooled over time)	**6**	**113**	**32.7**	**18.9 to 50.5**
pre-1975	3	74	36.8	26.1 to 48.9
1975 to 1979	1	3	30.8	14.7 to 53.4
1980 to 1984	1	16	33.7	15.2 to 58.9
1985 onwards	1	20	17.5	8.0 to 33.9
'mid-point date not calculable'	0	0	-	-
Unstratified (pooled over time) [a]	**18**	**1087**	**11.1**	**8.2 to 14.9**
pre-1975	4	79	15.1	8.2 to 26.2
1975 to 1979	4	296	12.0	6.7 to 20.6
1980 to 1984	4	423	13.5	8.4 to 20.9
1985 onwards	5	238	6.1	3.6 to 10.2
'mid-point date not calculable'	1	51	3.9 [b]	-

[a] All 20 case series only reported data for groups of patients with 'unstratified' defects.
[b] 95% confidence interval not available because the estimate was based on only one case series.

54   Changes in 30-day mortality with age at operation were investigated by classifying the average ages for case series into four groups, <12 months, 12 to 59 months, 60 to 119 months, 120 months or older and 'average age not reported'. After stratifying by anatomical defect and mid-point date, mortality in the 12 to 59 month group was similar to that for the <12 month group. However, mortality dropped by about two-thirds in the older groups (60 to 119 months: odds ratio = 0.33, 95%CI 0.20 to 0.54; 120 months and older: odds ratio = 0.35, 95%CI 0.09 to 1.30). Case series in which

the average age at operation was not reported had mortality similar to youngest age group.

Figure 4: 30-day mortality for c-AVSD case series separately for simple, complex and unstratified defect sub-groups

(a) Simple c-AVSDs
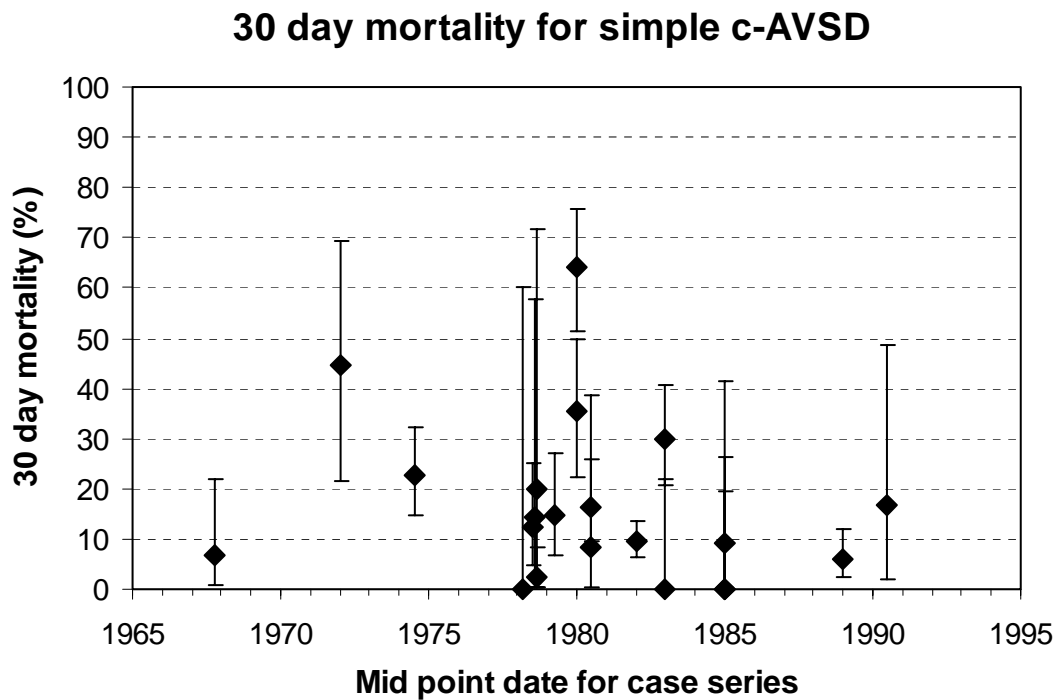
(b) Complex c-AVSDs
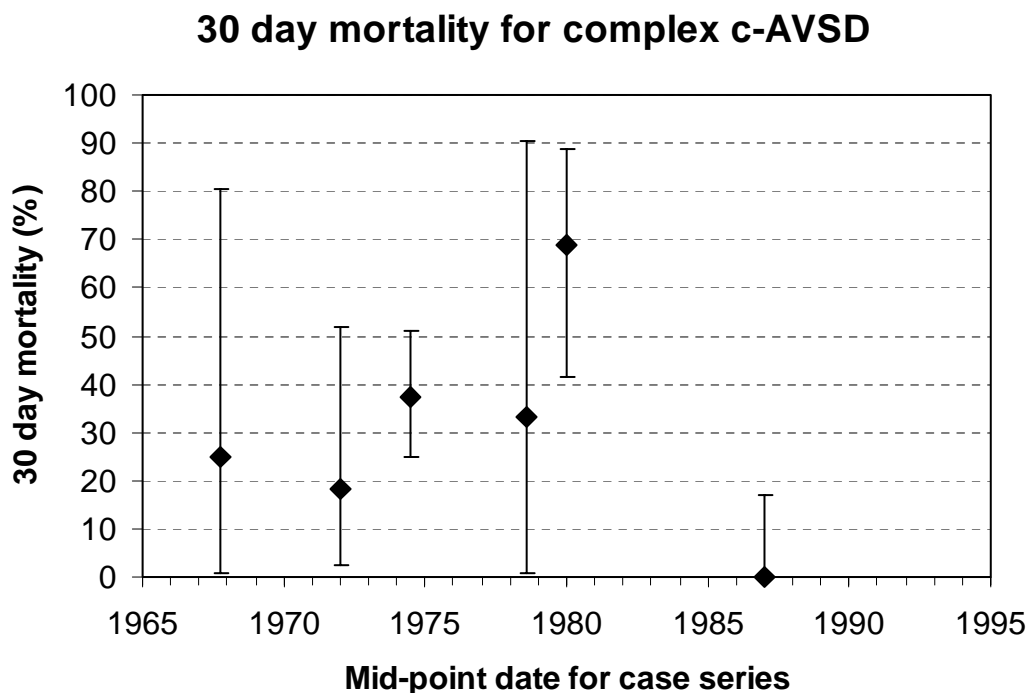
Figure 4 (cont.)

(c) Unstratified type c-AVSDs

30 day mortality for unstratified c-AVSD
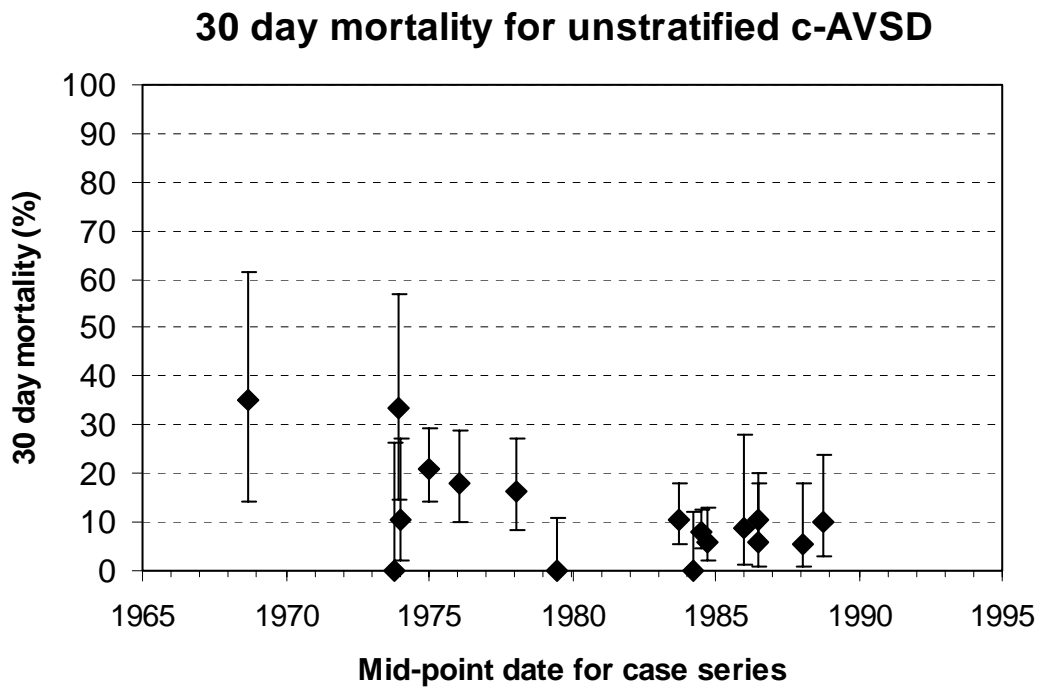
55   Multi-centre case series were associated with a reduction in 30-day mortality of about two thirds (odds ratio = 0.26, 95% CI 0.11 to 0.65). This was the only quality criterion found to be associated with mortality.

3.3.3 Total anomalous pulmonary venous drainage (TAPVD)

56   Individual 30-day mortality estimates and 95% confidence intervals by calendar time are displayed in Figure 5. Crude 30-day mortality pooled across all 19 case series was 24.0% (95% CI 16.4% to 33.5%)

Figure 5: 30-day mortality estimates and 95% confidence intervals for TAPVD case series (n=17). Two case series, which did not report start dates or duration, are not shown.
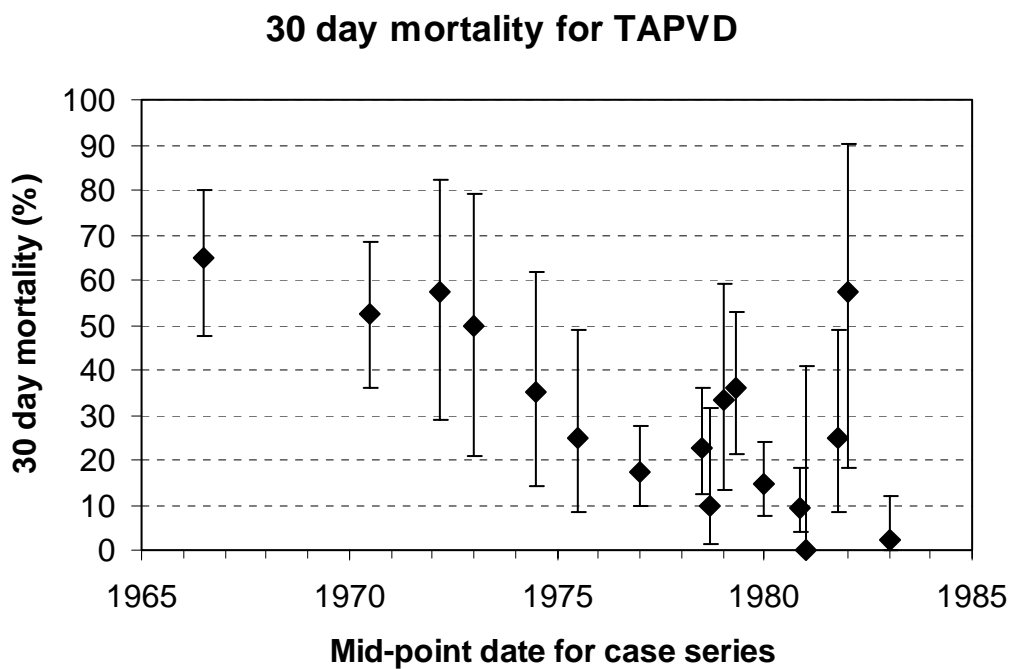
57   The majority of studies reported mortality separately for different anatomical sub-groups. Table 12 shows the numbers of case series and patients included in these series, 30-day mortality estimates and 95% CIs pooled across all available case series for each sub-group separately. Case series in which data were not stratified by anatomy, or where mortality was reported for an unstratified group of patients in addition to defined anatomical sub-groups, were included in the 'unstratified' stratum. Individual 30-day mortality estimates for each case series for each sub-group and 95% confidence intervals by calendar time are displayed in Figure 6. Note that the 30-day mortality estimates shown in Figure 6 do not take account of other differences

between case series, e.g. with respect to mid-point date for case series or the age of the patients.

Table 12: Case series of TAPVD reporting mortality separately for different anatomical variants

Anatomical variant	n (studies)	n (cases)	30-day mortality (%)	95% CI
Supracardiac (pooled over time)	**15**	**264**	**19.7**	**12.1 to 30.3**
pre-1975	5	67	43.6	34.7 to 52.9
1975 to 1979	4	81	13.9	10.9 to17.6
1980 to 1985	5	85	9.2	5.1 to 16.0
mid point date not reported	2	31	12.1	6.5 to 21.5
Cardiac (pooled over time)	**13**	**115**	**18.3**	**7.2 to 39.1**
pre-1975	5	25	43.9	21.4 to 69.2
1975 to 1979	4	26	14.1	7.9 to 23.9
1980 to 1985	3	49	9.3	4.3 to 18.9
mid point date not reported	2	15	12.2	5.5 to 25.0
Infracardiac (pooled over time)	**16**	**162**	**27.8**	**19.4 to 38.1**
pre-1975	5	20	63.6	49.3 to 75.9
1975 to 1979	5	65	26.8	20.5 to 34.2
1980 to 1985	5	66	18.6	11.9 to 27.9
mid point date not reported	2	11	23.7	13.9 to 37.5
Mixed drainage(pooled over time)[a]	**10**	**110**	**34.5**	**22.0 to 49.7**
pre-1975	4	60	51.8	41.3 to 62.2
1975 to 1979	2	9	18.4	11.3 to 28.5
1980 to 1985	3	36	12.3	6.2 to 23.0
mid point date not reported	1	5	16.1	7.9 to 30.2

[a] Three case series only reported data for a group of patients with 'mixed' drainage. A further seven case series reported data for a group of patients with 'unstratified' anatomy in addition to data for groups of patients in the other three strata.

58   The 30-day mortality for patients with cardiac, infracardiac/infradiaphragmatic and
      'mixed drainage' variants can be contrasted with the mortality for patients with
      supracardiac defects. There was no statistically significant difference between
      patients with supracardiac and cardiac anatomical defects, but patients with
      infracardiac/ infradiaphragmatic forms were estimated to have a mortality
      approximately 50% higher than for patients with supracardiac defects (odds ratio =
      1.57, 95% CI 0.95 to 2.59). Patients in the 'mixed drainage' stratum also appeared to
      have an increased 30-day mortality, approximately twice that estimated for the
      supracardiac group (odds ratio = 2.15, 95% CI 0.94 to 4.92).

59   Changes in 30-day mortality with calendar time were investigated by classifying the
      mid-point dates for case series into four groups, pre-1975, 1975 to 1979, 1980 to 1985
      and 'mid-point date not calculable'. After stratifying by anatomical defect, 30-day
      mortality for mid-point dates after 1975 was about one fifth of the pre-1975 level
      (1975 to 1979: odds ratio = 0.21, 95% CI 0.13 to 0.35; 1980 to 1985: odds ratio =
      0.13, 95% CI 0.06 to 0.27). Case series for which mid-point dates were not calculable
      had a low mortality, similar to the period from 1975 onwards. Mortality estimates for
      each sub-group and time period are included in Table 12.

60   Changes in 30-day mortality with age at operation were investigated by classifying
      the average ages for case series into four groups, 0-30-days, 31-90 days, >90 days,
      and 'average age not reported'. After stratifying by anatomical defect and mid-point
      date, there was a tendency for 30-day mortality to increase with increasing age,
      although the highest mortality was observed in case series, which did not report,
      average age. Patients aged >90 days at the time of operation were estimated to have
      about twice the mortality of patients aged 0-30-days although this increase in risk was
      not statistically significant (odds ratio = 2.08, 95% CI 0.68 to 6.40).

61   The requirement for authors to give a clear definition of 30-day mortality was
      associated with approximately a halving in mortality (odds ratio = 0.47, 95% CI 0.27
      to 0.80). This was the only quality criterion found to be associated with mortality.

Figure 6: 30-day mortality for TAPVD case series separately for different anatomical sub-groups

(a) Supracardiac TAPVD

30 day mortality for TAPVD with supracardiac defect

(b) Cardiac TAPVD

30 day mortality for TAPVD with cardiac defect
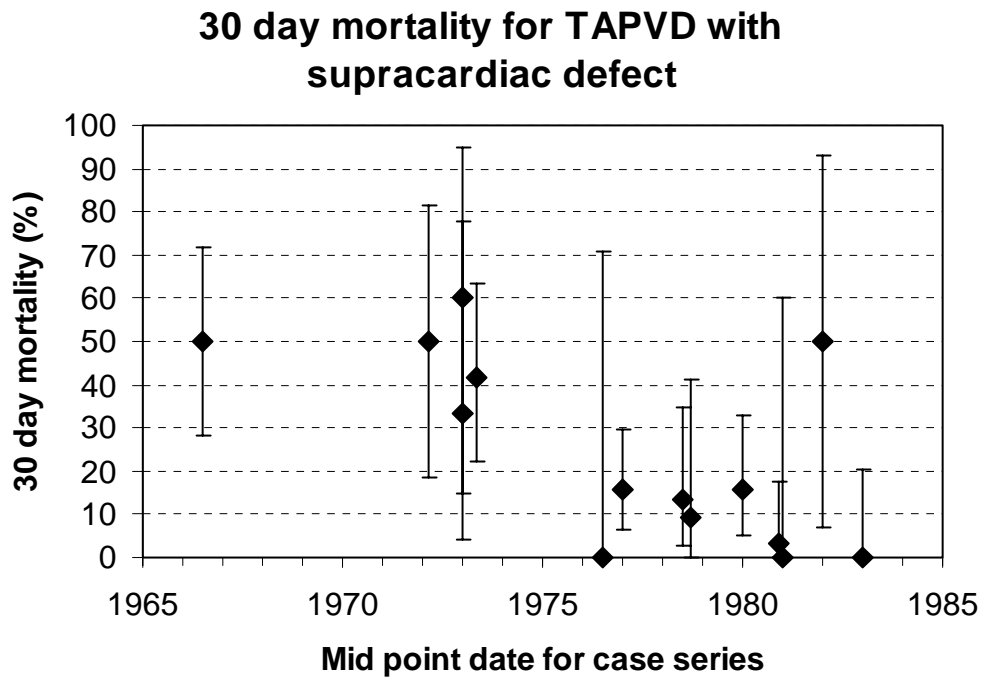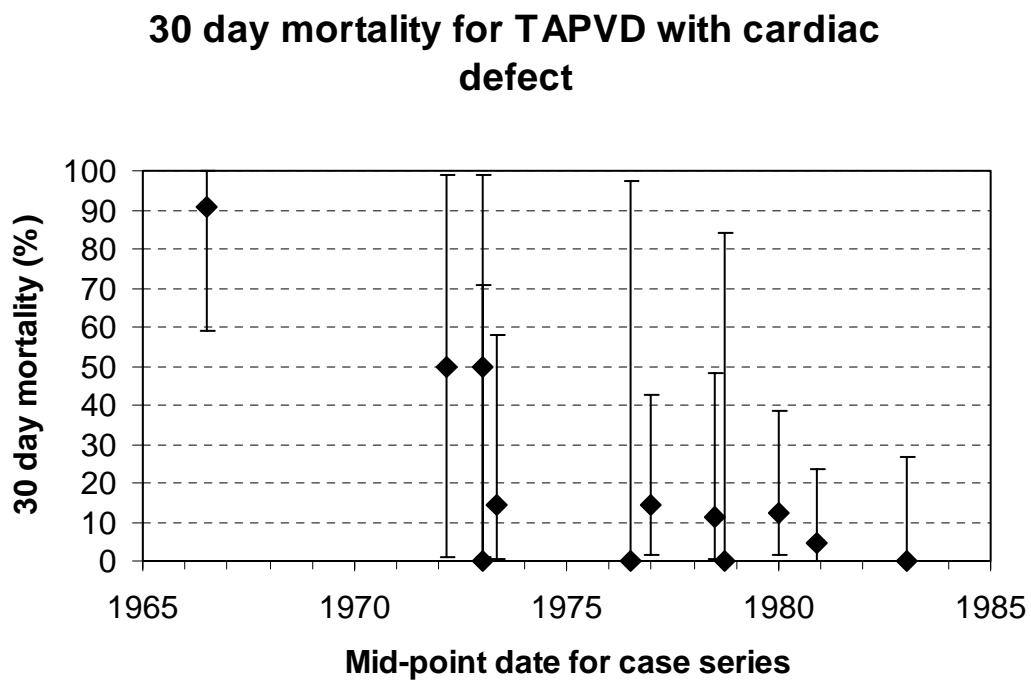
Figure 6 (cont.)

(c) Infracardiac TAPVD

30 day mortality for TAPVD with infracardiac defect

(d) Mixed drainage TAPVD

30 day mortality for TAPVD - unstratified or mixed anatomy
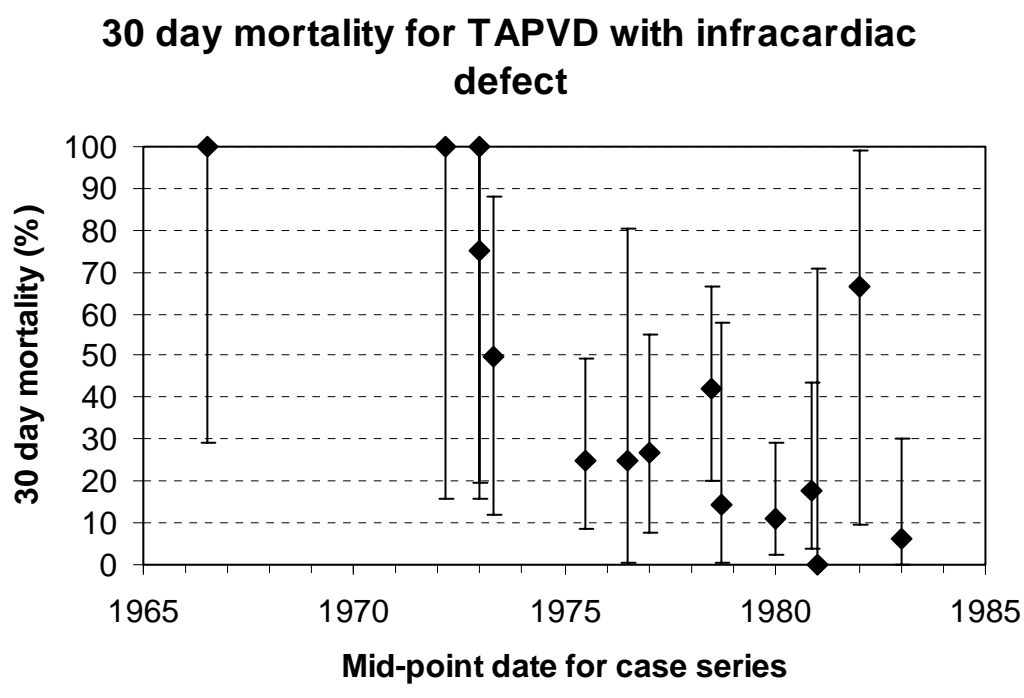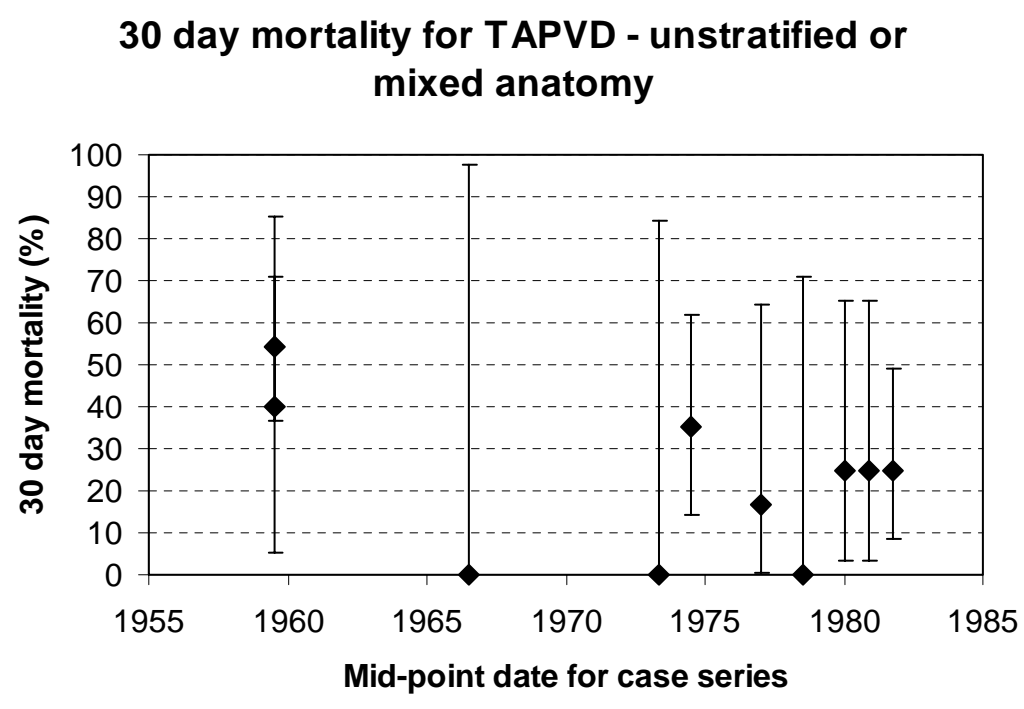
3.3.4 Truncus arteriosus

62 Individual 30-day mortality estimates and 95% confidence intervals by calendar time are displayed in Figure 7. Crude 30-day mortality pooled across all case series was 23.0% (95% CI 16.9% to 30.4%).

Figure 7: 30-day mortality estimates and 95% confidence intervals for truncus arteriosus case series (n=14). One case series, which did not report a start date, is not shown.
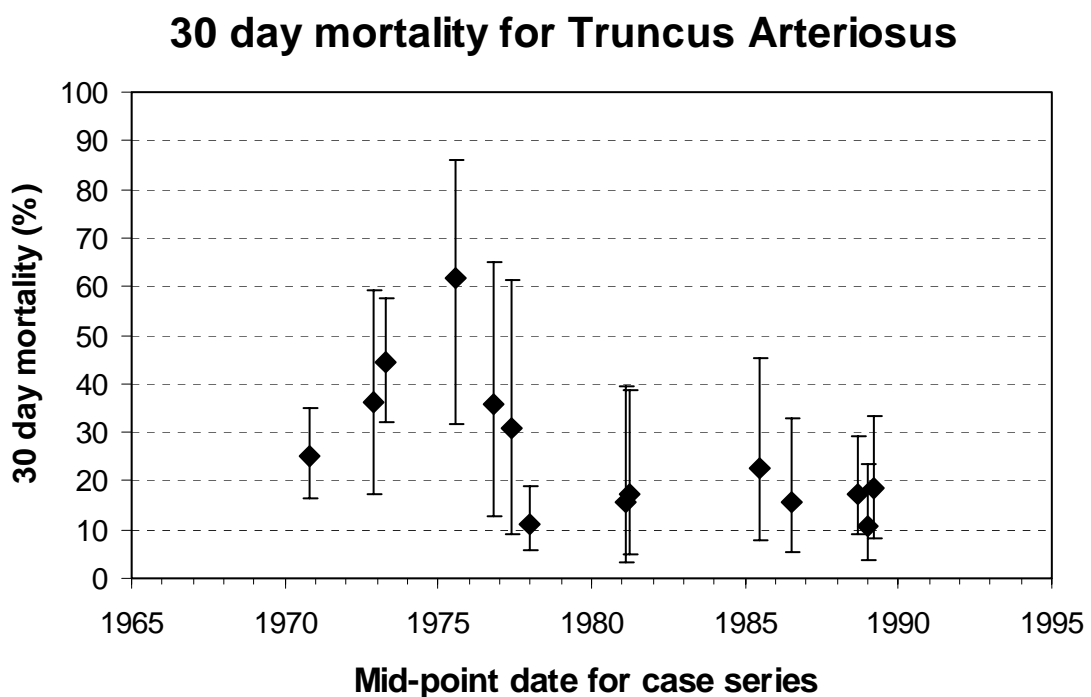
63 A minority of studies (6/15) reported mortality in sufficient detail to allow data to be extracted separately for simple and complex sub-groups (see section 3.2 for definitions of defects included in simple and complex categories); where this was not possible, data for case series were classified in the 'mixed' complexity sub-group. Table 13 shows the numbers of case series and patients included in these sub-groups, 30-day mortality estimates and 95% CIs pooled across all available case series for each complexity sub-group. Individual 30-day mortality estimates for each case series for each sub-group and 95% confidence intervals by calendar time are displayed in Figure 8. Note that the 30-day mortality estimates shown in Figure 8 do not take account of other differences between case series, e.g. with respect to mid-point date or the age of the patients.

64   The risk for patients with complex or mixed complexity defects can be contrasted with the risk for patients with simple defects. Patients with complex defects were estimated to have a mortality risk approximately double that for patients with simple defects (odds ratio = 2.65, 95% CI 0.73 to 9.66) although this finding was not statistically significant, probably because of the relatively small number of case series and patients. Patients in the 'mixed' stratum appeared to have a risk similar to patients with simple defects.

Table 13: Case series of truncus arteriosus reporting mortality separately for different complexity of defects

Anatomical variant	n (studies)	n (cases)	30-day mortality (%)	95% CI
Simple	**6**	**217**	**18.9**	**6.9 to 42.3**
pre-1975	1	65	38.6	26.4 to 52.4
1975 to 1979 [a]	0	0	-	
1980 to 1984	1	23	18.9	14.2 to 24.6
1985 onwards	4	129	9.0	4.7 to 16.5
mid-point date not reported [a]	0	0	-	-
Complex	**4**	**55**	**38.2**	**25.8 to 52.3**
pre-1975 [a]	0	0	-	-
1975 to 1979 [a]	0	0	-	-
1980 to 1984 [a]	0	0	-	-
1985 onwards	4	55	38.2	25.8 to 52.3
mid-point date not reported [a]	0	0	-	-
Mixed (pooled over time) [b]	**9**	**307**	**23.1**	**15.2 to 33.5**
pre-1975	2	114	30.6	21.8 to 41.1
1975 to 1979	4	140	20.0	8.6 to 40.0
1980 to 1984	1	19	14.0	9.1 to 21.1
1985 to 1990	1	22	6.5	2.0 to 19.4
mid-point date not reported [c]	1	12	33.3	-

[a]   Estimates and 95% CIs not available because no case series reported data for these strata.
[b]   All 9 case series only reported data for a group of patients with 'mixed' complexity defects.
[c]   95% confidence interval not available because the estimate was based on only one case series.

Figure 8: 30-day mortality for truncus arteriosus case series separately for simple, complex and unstratified defect sub-groups

(a) Simple truncus arteriosus

30 day mortality for simple Truncus Arteriosus

(b) Complex truncus arteriosus
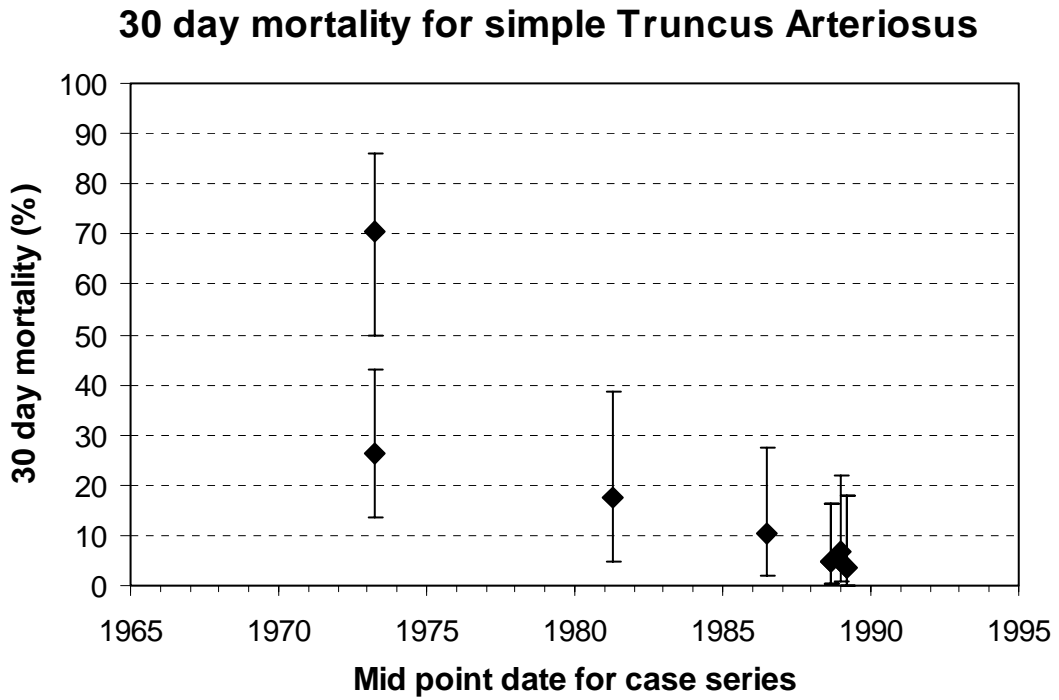
30 day mortality for complex Truncus Arteriosus
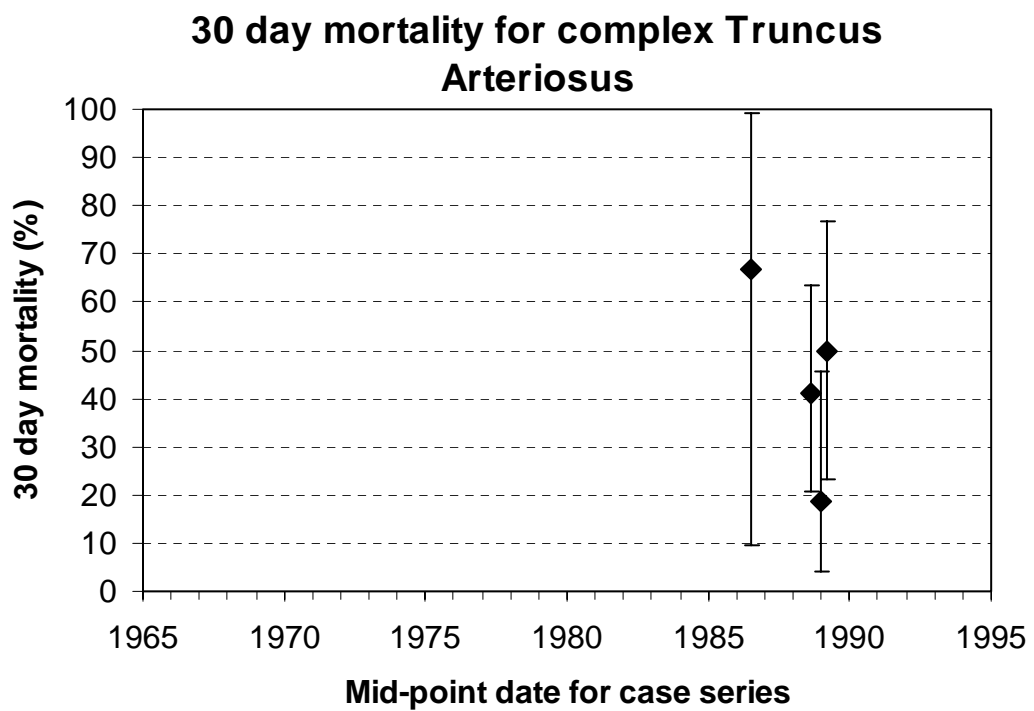
Figure 8 (cont.)

(c) Unstratified type truncus arteriosus

30 day mortality for unstratified Truncus Arteriosus
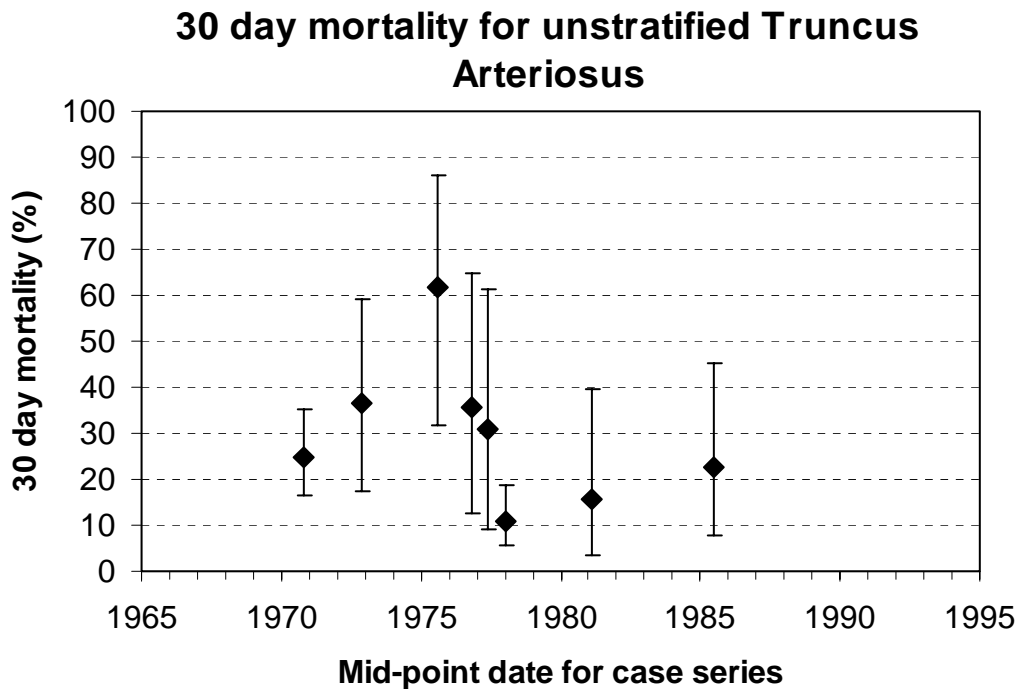
65   Changes in 30-day mortality with calendar time were investigated by classifying the mid-point dates for case series into five groups, pre-1975, 1975 to 1979, 1980 to 1984, 1985 onwards, and 'mid-point date not calculable'. After stratifying by anatomical defect, 30-day mortality decreased with time. The decrease was not significant for the 1975 to1979 period (odds ratio = 0.57, 95% CI 0.19 to 1.67) but was significant for later periods, dropping to about one third and one fifth of the mortality for the pre-1975 level (1980 to 1984: odds ratio = 0.37, 95% CI 0.25 to 0.55; 1985 onwards; odds ratio = 0.16, 95% CI 0.05 to 0.45). Case series for which mid-point dates were not calculable had mortality similar to the pre-1975 period. Including mid-point date in the analysis increased the mortality risk for complex defects relative to simple defects. Mortality estimates for each sub-group and time period are included in Table 13.

66   Changes in 30-day mortality with age at operation were investigated by classifying the average ages for case series into five groups, <3 months, 3 to 12 months, 12 to 59 months, 60 months or older, and 'average age not reported'. After stratifying by anatomical defect and mid-point date, there were no significant differences in mortality for different age groups. Part of the reason for failing to find any age effect

may be the small number of case series and patients contributing to each age group. The reporting of confidence intervals as a quality criterion was associated with a halving of mortality.

3.3.5 The Fontan Procedure

67   Individual 30-day mortality estimates and 95% confidence intervals by calendar time are displayed in Figure 9. Crude 30-day mortality pooled across all 58 case series was 14.8% (95% CI 12.7% to 17.1%).

Figure 9: 30-day mortality estimates and 95% confidence intervals for Fontan case series (n=58). Two case series, which did not report start dates or duration, are not shown.

30 day mortality for Fontan
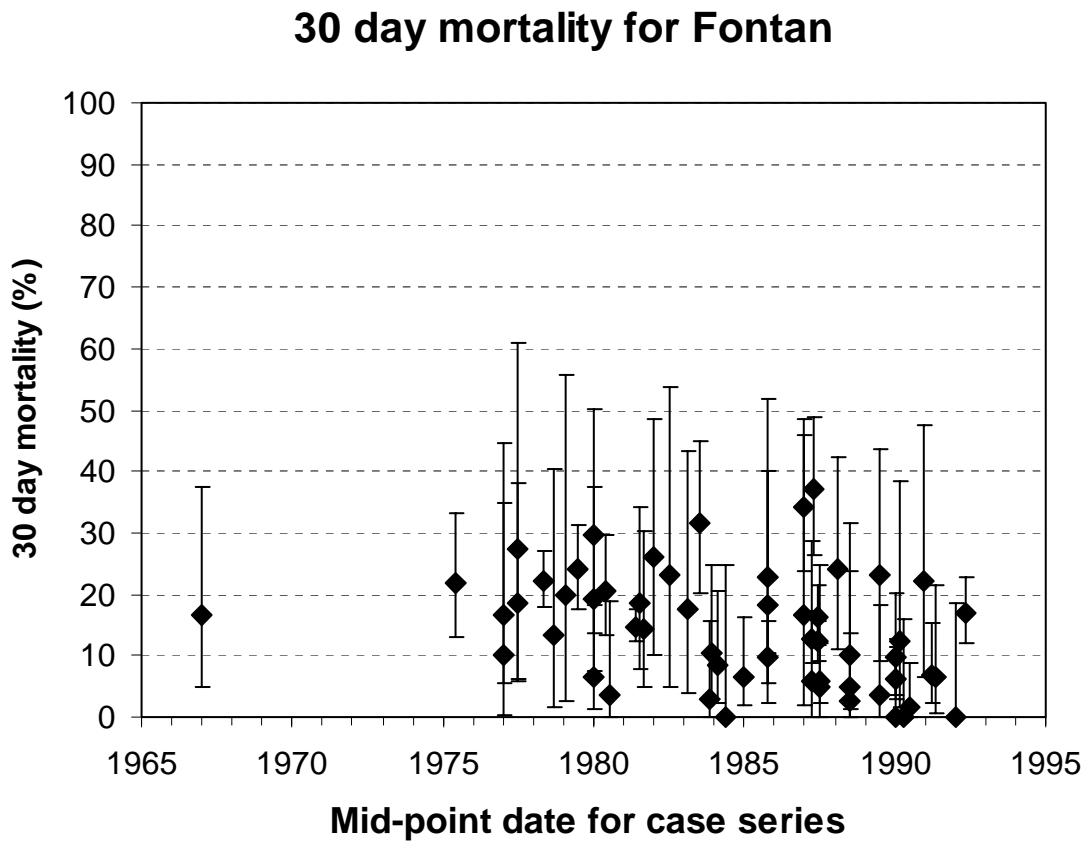
68   About half of the case series reported mortality separately for different types of defect treated by the Fontan procedure (see section 3.2 for definitions of defect sub-groups). Case series which reported mortality for some groups of patients that could not be classified into the categories that we chose, and case series that did not report mortality separately for any sub-groups, are included in the 'unstratified' defect sub-group. Table 14 shows the numbers of case series and patients included in these series, 30-day mortality estimates and 95% CIs pooled across all available case series for each sub-group separately. Individual 30-day mortality estimates for each case series for each sub-group and 95% confidence intervals by calendar time are displayed in Figure 10. Note that the 30-day mortality estimates shown in Figure 10 do not take account of other differences between case series, e.g. with respect to mid-point date or the age of the patients.

69   The mortality for patients with HLH, PA, SVO and unstratified univentricular heart defects can be contrasted with the mortality for patients with TA, often considered to be a more favourable defect treated using the Fontan procedure [41] Patients with HLH were estimated to have a mortality risk approximately three times that for patients with TA (odds ratio = 3.20, 95% CI 1.85 to 5.52); patients with PA had a similarly elevated mortality (odds ratio = 3.03, 95% CI 1.98 to 4.62). Patients with SVO also had higher mortality than patients with TA but only by a factor of about one and a half times (odds ratio = 1.65, 95% CI 1.26 to 2.16). Patients in the unstratified univentricular heart defect sub-group had a risk similar to patients with TA.

70   The data for HLH patients has a mid-point date of 1979, which appears to be inconsistent with the first known date for the Norwood procedure for HLH repair. This inconsistency has arisen because the six HLH cases represented by this point were part of a case series that extended from 1973-1985 and it was not possible to locate the HLH cases more precisely in time.

Table 14: Mortality estimates for Fontan case series by different defect types and by mid-point date

Anatomical variant	n (studies)	n (cases)	30-day mortality (%)	95% CI
Tricuspid atresia (TA)	**21**	**674**	**11.3**	**9.0 to 14.0**
pre-1980	6	326	14.4	11.0 to 18.6
1980 to 1984	8	159	9.2	6.2 to 13.5
1985 to 1989	3	92	8.0	5.8 to 10.8
1990 onwards	2	68	6.4	3.3 to 12.0
mid-point date not reported	2	29	9.8	2.8 to 29.2
Hypoplastic left heart (HLH)	**9**	**211**	**28.9**	**17.2 to 38.3**
pre-1980	1	6	43.4	29.1 to 58.7
1980 to 1984	3	17	31.7	19.2 to 47.4
1985 to 1989	5	188	28.2	18.6 to 40.4
1990 onwards	0	0	-	-
mid-point date not reported	0	0	-	-
Pulmonary atresia (PA)	**10**	**72**	**27.8**	**18.8 to 39.1**
pre-1980	4	34	33.7	22.8 to 46.5
1980 to 1984	4	26	23.5	14.1 to 36.6
1985 to 1989	4	11	20.7	13.0 to 31.2
1990 onwards	1	1	17.2	8.9 to 30.9
mid-point date not reported	0	0	-	-
Single ventricle – other (SVO)	**23**	**803**	**17.3**	**14.0 to 21.2**
pre-1980	6	285	23.6	16.5 to 32.5
1980 to 1984	9	202	15.7	10.7 to 22.5
1985 to 1989	6	154	13.7	9.7 to 19.0
1990 onwards	2	149	11.2	6.1 to 19.9
mid-point date not reported	1	13	16.6	5.1 to 42.5
Unstratified UVH defects [b]	**30**	**2649**	**13.4**	**10.9 to 16.5**
pre-1980	5	496	20.7	16.4 to 25.9
1980 to 1984	8	461	13.7	10.3 to 17.9
1985 to 1989	12	1211	11.8	9.8 to 14.2
1990 onwards	9	481	9.7	6.2 to 14.8
mid-point date not reported	0	0	-	-

[a] Estimates and 95% CIs not available because no case series reported data for these strata.
[b] 26 case series only reported data for a group of patients with 'unstratified' defects; a further 4 reported data for a group of patients with 'unstratified' defects in addition to data for at least one group of patients with a specified defect.

Figure 10: 30-day mortality for Fontan case series separately for simple, complex and unstratified defect sub-groups

(a) Tricuspid atresia

30 day mortality for Fontan for tricuspid atresia

(b) Hypoplastic left heart
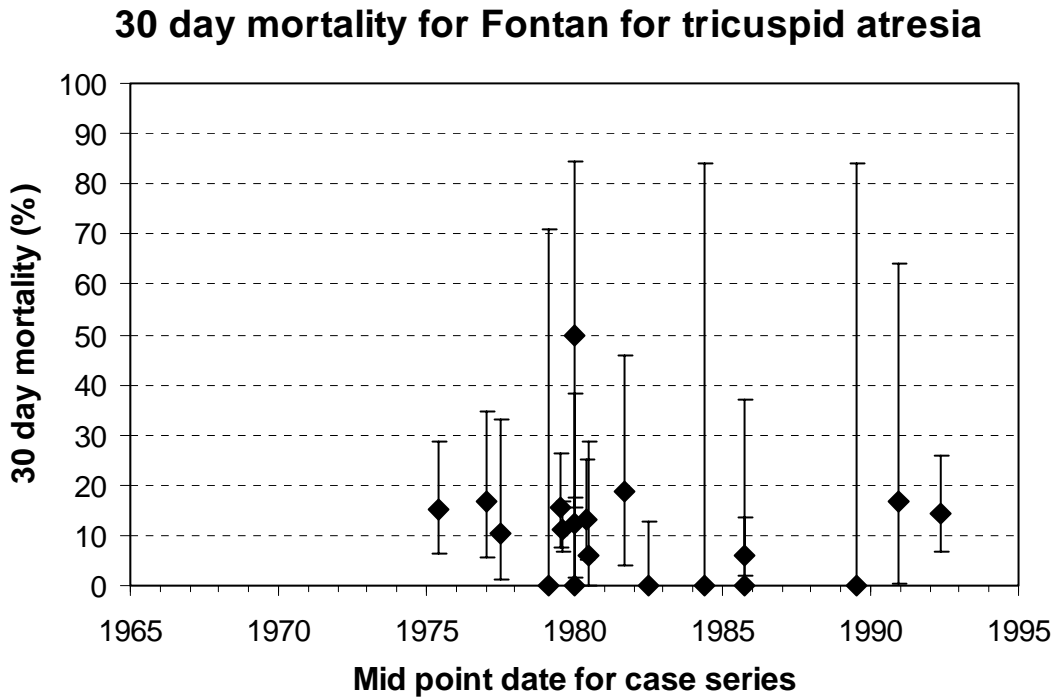
30 day mortality for Fontan for hypoplastic left heart
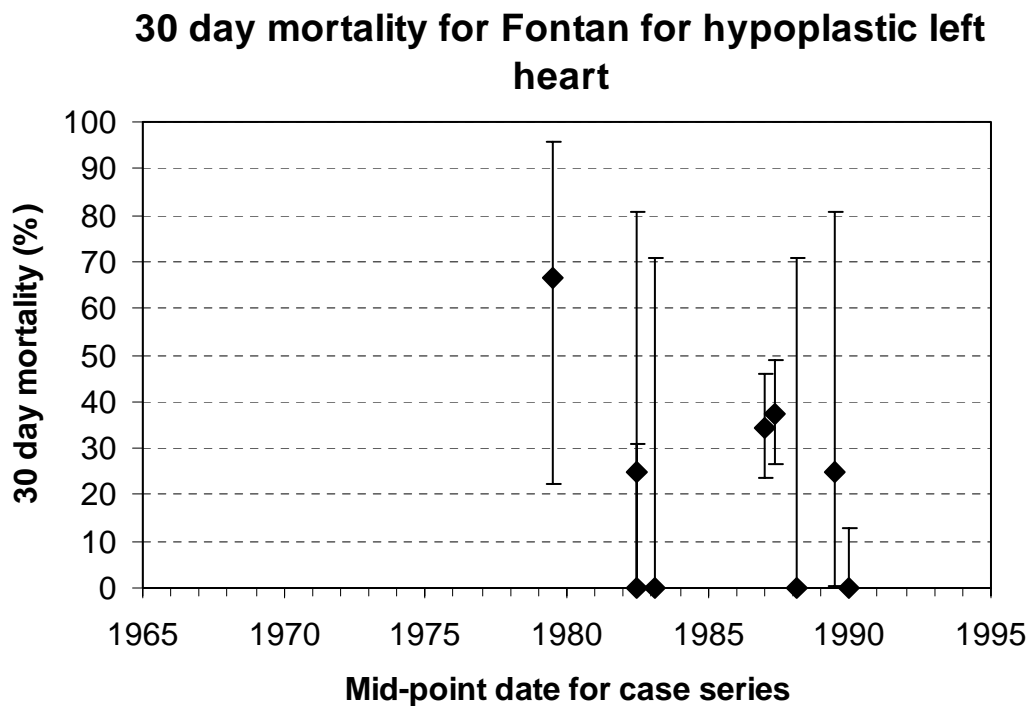
Figure 10 (cont.)

(c) Pulmonary atresia

30 day mortality for Fontan for pulmonary atresia

(d) Single ventricle, other
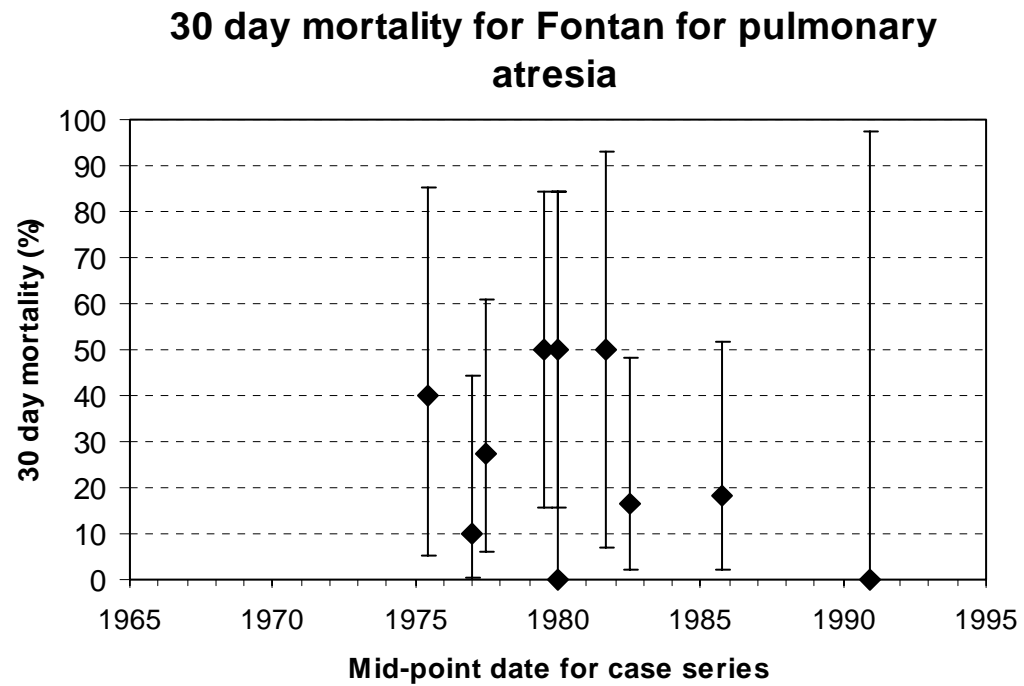
30 day mortality for Fontan for single venticle, other
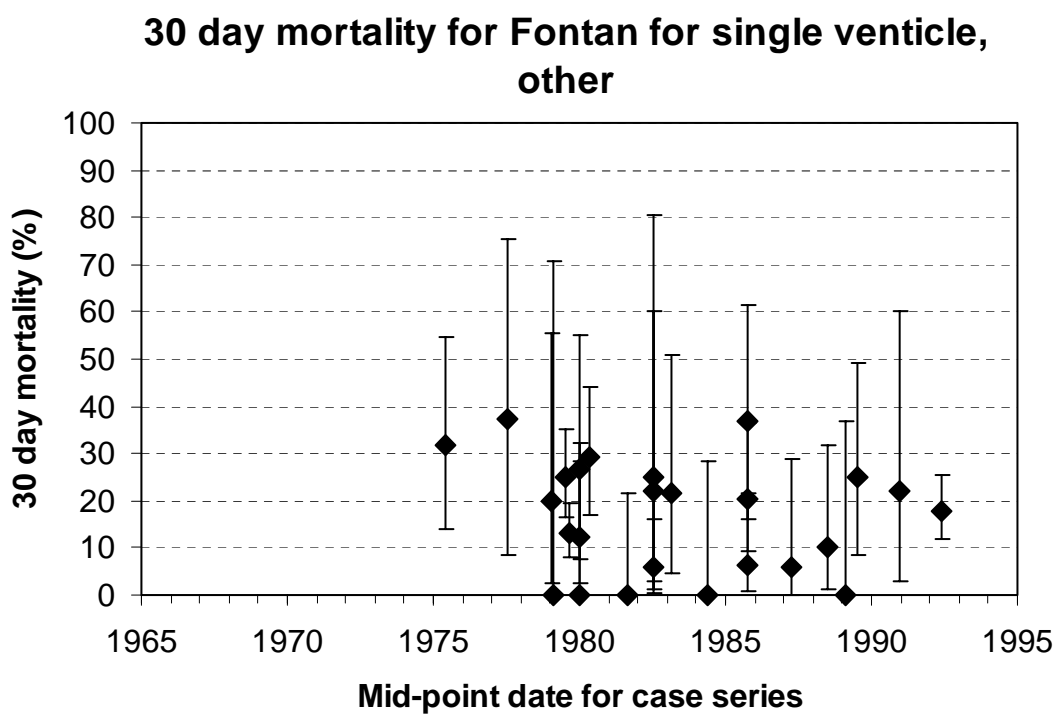
Figure 10 (cont.)

(e) Unstratified univentricular heart defects

30 day mortality for Fontan for unstratified defects
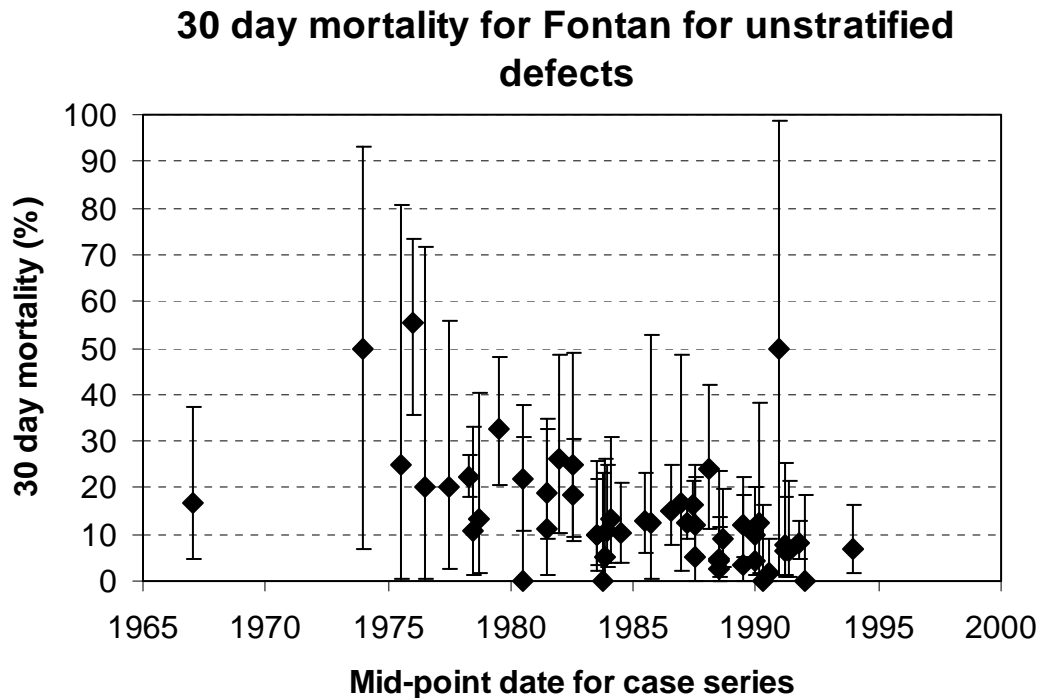
71   Changes in 30-day mortality with calendar time were investigated by classifying the mid-point dates for case series into five groups, pre-1980, 1980 to 1984, 1985 to 1989, 1990 onwards, and 'mid-point date not calculable'. After stratifying by anatomical defect, 30-day mortality decreased steadily with time, with mortality from 1985 onwards being about half that before 1980 (see Table 15). Case series for which mid-point dates were not calculable had mortality similar to the 1980-1984 period. Mortality estimates for each sub-group and time period are included in Table 14.

72   The change in 30-day mortality with age at operation was investigated by classifying the average ages for case series into four groups, <3 years, 3 to 5 years, 6 to 8 years, 9 years or older, and average age not reported. Age at operation was strongly correlated with the mid-point date for case series, with the 'average age at operation' decreasing steadily over time. After taking account of type of defect and mid-point date, mortality for the 6 to 8 years age group was approximately twice the mortality for the youngest group (6 to 8 years: odds ratio = 1.91, 95% CI 1.03 to 3.53). Mortality for

the oldest group and unknown age group was similar and not significantly higher than for the youngest group. None of the quality criteria was associated with 30-day mortality.

Table 15: 30-day mortality by mid-point date for Fontan case series, after taking account of sub-groups with different combinations of congenital defects

Mid-point date	n (studies)	n (cases)	odds ratio	95% CI
Pre-1980	10	1147	1.00	
1980-1984	17	865	0.61	0.40 to 0.92
1985-1989	18	1656	0.51	0.36 to 0.72
1990 and after	11	699	0.41	0.22 to 0.77
Mid-point date unknown	2	42	0.65	0.16 to 2.51

3.4   Longer-term outcomes reported in the study

73   The main focus of this review was to report 30-day post-operative mortality, so papers selected were chosen to report early outcomes. We excluded those that reported only late results. It was not feasible to search for and review literature on longer-term outcomes within the remit of this review.

74   In addition to 30-day mortality rates other outcomes were sometimes described. Early post-operative complications such as bleeding and wound dehiscence were commonly reported as were more severe complications, arrhythmia, deterioration in functional and neurological status, and the need for re-intervention.

75   Late deaths attributable to operation-related factors and non-cardiac disorders were also reported in a small subset of papers but few had sufficient follow-up times to comment on both early and late outcomes.

76   No attempt was made to extract such detailed morbidity data, however, because the quality and detail of reporting throughout the eligible papers was inconsistent. Morbidity and outcomes other than mortality were often described in general terms or listed in tables and were unattributable to specific members of the original study population.

77   Because of logistical difficulties in following up patients and in defining outcomes
        other than death consistently across studies, we believe that our experience of the
        reporting of such outcomes in the literature we reviewed was not atypical. This
        implies that reviewing other outcomes would not have yielded meaningful
        quantitative estimates of their frequency.

3.5   Communication of surgical risk

78   Papers that were reviewed did not comment on how surgeons should communicate
        risk to their patients and their families. However, this review has demonstrated
        variations in 30-day mortality for different clinical sub-groups that, at the outset, were
        hypothesised to have varying risks of mortality by expert clinical advisers to the
        review. Although the pooled estimates of mortality reported in this review may not
        generalise to other centres that do not collect case series (4.2), the relative differences
        in mortality between clinical sub-groups are more likely to do so. In principle,
        therefore, surgeons should consider discussing how the specific nature of a patient's
        congenital anomaly affects the risk of mortality, relative to the 'average' risk.

79   Although the review has demonstrated empirically variations in 30-day mortality for
        different clinical sub-groups, clinical advisers to the review also stressed the
        importance of physiological factors in determining the risk of mortality. These
        factors were rarely reported in the papers that were reviewed, precluding any
        quantitative estimation of the risk that they confer. The importance of physiological
        factors in determining the risk of mortality may be more important than anatomical
        factors in some cases.

80   The review has also shown how outcomes have improved with the passage of time.
        This finding emphasises that surgeons should collect personal data on the outcomes of
        their operations and, ideally, contribute these data to a larger national pool, e.g. UK
        Cardiac Surgical Register. Surgeons should not assume that recent personal data
        provide the best guide to outcome, since the relatively small number of patients
        treated by one surgeon will give rise to greater random fluctuations in outcome.
        There are established statistical methods for weighting information from local and
        national sources appropriately. It should be stressed that collection of data to

characterise patients and their outcomes must be carried out in accordance with established data definitions.

81   The substantial variation in mortality between case series illustrates the dangers of using risks reported in the data to communicate expected outcomes. Some of this variation arises from sampling error but, almost certainly, some arises from selection biases and centre-specific factors.

4.   Discussion

4.1   Summary of key findings

82   The review has met its first objective of identifying and synthesising evidence on 30-day mortality risk. Broadly, there were many case series, reporting data for over 2000 individuals, for three operation /defect types: (a) TGA, (b) c-AVSD and (c) Fontan. There were relatively few case series, reporting data for about 600 individuals, for TAPVD and truncus arteriosus. Pooled estimates of 30-day mortality were lower for the three more commonly reported operation types (TGA - 11.2%; c-AVSD - 14.7%; Fontan - 14.8%) than for the two more rarely reported defect types (TAPVD – 24.0%; truncus arteriosus – 23.0%) although the confidence intervals for these estimates often overlapped.

83   In relation to the second objective, the review has demonstrated that some of the variation in estimates for 30-day mortality between case series for a particular operation /defect type can be explained by case-mix, i.e. clinical sub-groups considered to be important by clinical experts prior to analysing the data. The relative differences in mortality for different sub-groups were broadly consistent with the experience of clinical experts. The review has also demonstrated consistent improvements in mortality over time for all five operation / defect types in the types of centres that report case series.

84   We pursued the third objective, of trying to assess the research quality of the published case series in order to investigate whether quality was associated with mortality, but without being able to draw any clear conclusion. Reviewers often find that RCTs that have been carried out to a very high standard (judged against accepted quality criteria) yield smaller effect sizes than low quality RCTs, implying that poor research quality introduces biases and consequent overestimation of the effect size. By analogy, we hypothesised that case series of poor research quality would tend to report lower mortality as a result of selection biases. This hypothesis was not supported by the findings. Multi-centre studies (regarded as having good research quality) were associated with increased mortality for TGA but decreased mortality for c-AVSD; an explicit statement about recruitment of consecutive patients (regarded as having good research quality), the criterion most obviously related to selection bias,

was associated with increased mortality only for TGA. Other criteria (clear case definition and reporting of confidence intervals) were each associated with a decrease in mortality on one occasion, for TAPVD and truncus arteriosus, respectively. It is unclear whether the criteria we chose to assess (adapted from other reviewers) lacked discrimination as indicators or research quality or whether there truly was no association between research quality and mortality. The absence of any association between the indicators of research quality that we assessed and mortality imply that the pooled estimates of mortality reported in section 3.3 remain the best estimates of mortality available from the literature.

85   Authors of the papers reviewed did not comment directly on risk factors that they take into account and communicate to patients and their families. The review has demonstrated the importance of some clinical sub-groups and has attempted to quantify their relative risk. These sub-groups were defined at the outset on the basis of the experience of clinical advisers to the review team and one might therefore expect surgeons with similar experience to already know about the importance of these sub-groups. We were unable to investigate the risk conferred by physiological factors which clinical advisers emphasised are likely to be as important, and sometimes more important, than anatomical ones. Variation between case series highlighted the need for individual surgeons to monitor their practice and to contribute these data to a national database. There are well recognised methods for weighting local and national data in estimating the current risk in a local setting.

86   Several issues need to be taken into account with respect to interpretation of the research evidence, the sixth objective. Interpreting the evidence is very important in reconciling the specific objectives of the review (see paragraph 4) with the aims of the Inquiry when the review was commissioned (see paragraph 3). Our interpretation relates directly to the question about how well the review summarises the knowledge base that might have been available to Bristol clinicians during 1984-1995. These issues can be considered as a hierarchy.

87   First, there are issues concerning the generalisability of the mortality estimates reported in case series, i.e. the extent to which case series estimates represent a

realistic target that practising surgeons should aim to achieve. This issue is considered in more detail in section 4.2.

88   The second level of the hierarchy concerns the accessibility of evidence. It is implausible to us that surgeons should be expected to have easy access to and to read regularly all of the journals in which relevant evidence might be published. The difficulty of keeping up-to-date was well illustrated by one of the clinical expert advisers to the Inquiry. Having ranked relevant peer-reviewed journals in order of importance with respect to developments in the field of paediatric cardiac surgery, he commented:

> *"I wouldn't like to suggest that any [practising] surgeon could possibly keep in touch with all these journals! If I manage to scan through the first three every month I feel I am doing well."*

89   The third issue concerns the synthesis of available evidence. Even if a surgeon were to have read all of the relevant evidence that we have reviewed, it is extremely unlikely that he or she would have the expertise to synthesise the evidence as we have done. To our knowledge, this is the first example of a medical systematic review which has attempted to pool evidence from case series. The importance of synthesis can be illustrated by analogy with early meta-analyses of RCTs, for example of the use of corticosteroids in women expected to deliver prematurely to reduce the risk of respiratory distress in the infants after birth [42]. Such meta-analyses demonstrated how evidence in the literature was not accessible to practising clinicians; in effect, these meta-analyses provided 'new' evidence by finding and synthesising the existing literature in a way that no practising clinician could have been expected to do at the time.

90   The fourth issue concerns the time lag that has been described between the publication and widespread uptake of evidence. This point was demonstrated by Antman et al., who showed how up-to-date textbook recommendations of effective health care tended to lag behind up-to-date evidence from meta-analyses of the literature by about 10 years [43]. General concern about slow uptake of evidence has led to projects to promote implementation of evidence in several areas of health care [44,45]. It may be legitimate to criticise health care professions for their conservatism

in this respect, but it is important to acknowledge that this tendency is widespread and not restricted to a minority of practitioners.

4.2   Generalisability of the evidence

4.2.1   Atypical centres

91   One reason for questioning the generalisability of the mortality estimates from case series is the tendency for such studies to be published by specialist centres. This tendency was clear in the literature that we reviewed. About one third of all of the case series that were finally included were published from only seven centres, namely:

- Boston Children's Hospital, Boston, USA

- Children's Memorial Hospital, Chicago, USA

- Great Ormond Street Hospital for Sick Children, London

- University of California Los Angeles School of Medicine, Los Angeles, USA

- Mayo Clinic and Foundation, Rochester, USA

- Royal Children's Hospital, Melbourne, Australia

- University of Michigan School of Medicine, Michigan, USA

Each of these centres published case series for at least three of the five operation /defect types.

4.2.2   Patient selection

92   Papers describing what purport to be 'consecutive' cases are sometimes difficult to interpret. It would be a fallacy to describe patients who have a Fontan procedure as representative of all those with a univentricular heart defect as this is very much the final stage of a series of palliative operations, each of which carries high mortality risks. Patients who survive to the stage where they undergo a Fontan procedure are likely to be a highly selected group, who are fitter or have simpler manifestations of univentricular heart defects than those who die before reaching this stage.

93   There may also be a difficulty in interpreting consecutive case series for other operation types or defects. Some papers reported a consecutive series of patients with a highly specific defect and data from these papers were included in one of the sub-groups for a particular type or defect. It is possible that these case series may have

been so specialised that the patients were not typical of the sub-group to which they were allocated.

4.2.3 Publication bias

94   Inevitably, the review of case series evidence can be subject to publication bias. The first difficulty arises from the fact that institutions which publish large case series are atypical and more likely to be 'centres of excellence' with lower than average operative mortality rates (see also 4.2.1). There may also be a tendency for centres to select cases in a way that minimises mortality, e.g. by including non-consecutive patients or by carefully choosing the reporting period to exclude unfavourable results. Publication bias may be most serious with respect to the findings of this review in the context of trends in 30-day mortality over time; for example, once an implicit 'standard' has been set through previous publications, centres may choose to publish only those case series which give better results.

95   Statistical methods have been developed to attempt to quantify the effect of publication bias in meta-analysis of randomised controlled trials. [46,47]. Funnel plots, plotting effect size against sample size, will be asymmetrical if publication bias is present. However, this method has not been recognised for use with case-series data. Hence, we have not applied this method to our data. Moreover, the concept of unpublished data has a different meaning in the two contexts of case series and randomised controlled trials. Data for unpublished randomised controlled trials are likely to exist in some form whereas data are unlikely to be available in a useable format from centres that have not published case series.

4.3 Limitations of review

4.3.1 Literature searching

96   Although every effort was made to include all relevant keywords and acronyms, describing both defects and operative procedures, surgical developments and changing terminology will almost certainly have led to our search strategies missing some relevant studies. Further elaboration of the search strategies is likely to have yielded more irrelevant citations, though, as well as occasional relevant ones so, given the time-scale for the review, we believe our strategies represent an efficient compromise.

97   We were constrained by the inaccuracy of the MeSH headings ascribed to papers. Initially we chose to limit the number of papers using the MeSH headings 'thoracic and cardiac surgery' but on further investigation noted that less than one third of total papers found, using all keywords and acronyms for a defect/operation type, were indexed under these MeSH headings. A more commonly ascribed MeSH term was 'Heart-defects, congenital' which we used with the sub-heading 'surgery'. Other sub-headings, e.g. 'mortality' may have found more relevant papers.

98   Frequently, searches identified a paper where the keyword pertained to an associated defect, and not the primary defect or operation. This led either to re-classification or exclusion.

4.3.2 Data extraction

99   Ages and weight at operation where not routinely or consistently recorded in publications. Both means and medians were presented, as were age ranges. In the database, means and medians were used interchangeably, whilst midpoints were used in the case of narrow ranges. If age ranges were very large, and no sensible mid point could be determined, no age value was entered.

100   Numerical and computational mistakes within the paper and inconsistencies between the main text and the abstract were common. In such cases, information was extracted from the text, not the abstract.

101   For rare operation types, case series may be small. For operation to repair truncus arteriosus, a large number of papers were not selected from the 151 (see Appendix E) as they were indexed as case reports. A further 13 papers were discovered to be case reports when full text versions were read.

4.3.3 Repeat publication of case-series data

102   The publication of interim reports and subsequent duplication of data was a significant problem (especially for the Fontan procedure) and resulted in the exclusion of 51 publications.

103   We excluded publications where data were clearly presented more than once. Those with overlapping time periods were included, otherwise large periods of data collection would often be lost. Unless we were certain that the same data were repeated in more than one paper, the case series remained in the dataset. In many cases, the only way to compare publications was to look at the descriptions of patients who had died.

104   The problem of duplicate publications is familiar to reviewers carrying out meta-analyses of randomised control trials and the Cochrane Collaboration has strongly criticised this practice. If anything, we believe that the problem is more acute when reviewing case series since it was our experience that authors rarely acknowledged that data had been published before or referenced previous publications. If data collection start dates and duration are not reported, or two papers report for overlapping periods, it is impossible to exclude duplicate data.

4.3.4   Limitations of data analysis

105   For some operation / defect types we suspect that there are complicated associations between clinical sub-group, mid-point date and age at operation. For example, the average age at which an operation is carried out may have increased with time and may also vary across clinical sub-groups, e.g. with the Fontan procedure. It is possible that our modelling approach may not fully reflect these complexities.

106   We judged that mid-point date for case series was the most appropriate measure of calendar time to investigate. However, this approach has the disadvantage that it is difficult to know when estimates of mortality for particular time periods that we have derived are likely to have been published, i.e. to have been available to surgeons. The distribution of time lag to publication after completion of data collection had a median of one to two years across operation / defect types but was positively skewed. It must also be remembered that mid-point date depended on the duration of studies, which was not reflected in the time lag to publication.

4.4   Context setting

107   We originally proposed to attempt to quantify the generalisability of the data we extracted from publications, in order to clarify the relevance of any comparison of

the mortality estimates with those observed at the Bristol Royal Infirmary.

108   We intended to do this by plotting annual mortality from the UK Cardiac Surgery Register (UKCSR) for the 5 operation types against the published data we extracted. However, other evidence commissioned by the Inquiry [48] has implied that, particularly in the earlier years, there was likely to have been considerable mis-classification of operations by type, by those contributing to the UKCSR. This commissioned evidence also questioned the validity of the mortality data reported in the UKCSR. We concluded that it would therefore be inappropriate to make such comparisons.

109   We have not compared the mortality estimates derived from the literature with data for the Bristol Royal Infirmary obtained by the Inquiry for two reasons. First, for the reasons given above, we have no method of judging the extent of the difference between 'best achievable' results (as reported in this review) and the results that might be expected in usual practice. Without such a yardstick, it is impossible to comment on the difference between the results in the literature and the results observed at the Bristol Royal Infirmary. Second, the Bristol Royal Infirmary data are not broken down by clinical subgroups and do not provide sufficient information to allow adjustments for case-mix. Without knowing even the relative frequencies of children in different clinical sub-groups, let alone the mortality results for each sub-group separately, we believe it is inappropriate to make any direct comparison.

5   Conclusions and recommendations

110   Case series on five open-heart operations / congenital anomalies have been reviewed systematically and the data have been synthesised. The pooled 30-day mortality estimates (at a particular point in time) are likely to represent 'best achievable performance' rather than the performance to be expected in everyday practice.

111   There was clear evidence of differences in mortality between clinical sub-groups within operation / defect types. Although there is always the possibility that these relative differences do not generalise to usual practice, this evidence probably justifies trying to define these clinical sub-groups unambiguously in the future, as a simple measure of case-mix.

112   For all five operation / defect types, there was evidence that mortality has decreased over time, with mortality in the early 1990s less than 50% of the mortality observed in the 1970s. This trend may in part reflect the influence of a surgical learning process, the implications of which have been recently discussed [49], that often occurs with a new technology, presumably arising from greater clinical experience and advances in instrumentation. The extent to which this learning curve might be accelerated when a centre starts to perform an operation is unclear.

113   We believe that this is the first attempt to synthesise data from case series. Case series are usually regarded as the weakest kind of published evidence and reviewers have traditionally cautioned against any attempt to pool such evidence quantitatively. Although we have similar reservations about the generalisability of the absolute pooled mortality estimates that are reported in the review, we believe that relative differences in mortality between clinical sub-groups are likely to be more robust. We hope that this review will stimulate a methodological debate about the research questions that systematic reviews of case series may be able to address.

114   A number of methodological principles, well established in the context of systematic review of RCTs, were difficult to apply to a systematic review of case series. In addition to a debate on the possible applications of systematic reviews of case series,

detailed consideration needs to be given to strategies for improving their validity. If case series are to be synthesised in the future, it is vital that authors of the original papers cease to publish the same data in more than one publication. In our view, journal editors should consider making an explicit statement by authors to this effect a requirement for publication.

115   The review was commissioned primarily with the aim of understanding better the knowledge base that might reasonably have been expected to be available to the Bristol clinicians during 1984-1995. We have identified and synthesised the knowledge that existed but have pointed out, by analogy with other literature on systematic reviews, that it is probably unrealistic to have expected the Bristol clinicians to be aware of this knowledge. We propose that the paediatric surgical community should judge the relevance of the knowledge presented in the review to everyday practice.

116   Given the reservations about the generalisability of the evidence, it is important for individual surgeons to collect high quality data on their own practices in order to be able to obtain truly informed consent from patients and their families. An attempt to provide clear definitions and collect multicentre data on a number of benchmark lesions in paediatric cardiac surgery was made by Stark et al [50] and represents a first attempt to collect and compare high quality individual centre data.

117   It is important to recognise however, that the appropriate risk for a surgeon to communicate to patients and their families should be a weighted combination of his own and national data, not his personal data alone. Therefore, surgeons should contribute their data to a national database. Data collection should be carried out in accordance with recognised standards and definitions.

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7   References

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8. Appendices

Appendix A: Origin of papers included in this review

Name of journal article	TGA	Truncus Arteriosus	AVSD	TAPVD	Fontan	Total
Annals of Thoracic Surgery	4	3	9	3	15	34
Circulation	3	1	0	2	6	12
Journal of Cardiac Surgery	0	0	3	0	1	4
Journal of Thoracic and Cardiovascular Surgery	16	5	13	3	19	56
Thoracic Cardiovascular Surgeon	4	1	1	2	3	11
Other journals (accounting for less than 8 total articles for all operations)	7	5	13	9	14	48
Total relevant articles for each operation type	34	15	39	19	58	165

Appendix B: Medline Silverplatter search history for transposition of the great arteries

No.	Records	Request
1	142861	arterial
2	7041	switch
3	320	arterial switch
4	4144	explode "Transposition-of-Great-Vessels"/ all subheadings
5	9546	Transposition
6	113696	great
7	100954	arteries
8	1809	Transposition of great arteries
9	905	TGA
10	5051	#9 or #8 or #4 or #3
11	8623465	PY < "1996"
12	4836	#10 and (PY < "1996")
13	7041475	PY > "1974"
14	3634	#12 and (PY > "1974")
15	471295	explode "Infant"/ all subheadings
16	259933	explode "Infant-Newborn"/ all subheadings
17	471295	#15 or #16
18	1964	#14 and #17
19	17629	explode "Heart-Defects-Congenital"/ surgery
20	1284	#18 and #19
21	6663681	LA = "ENGLISH"
* 22	879	#20 and (LA = "ENGLISH")

Appendix C: Medline Silverplatter search strategy for complete atrioventricular septal defects

No.	Records	Request
1	290	explode "Endocardial-Cushion-Defects"/ all subheadings
2	12591	atrioventricular
3	25588	septal
4	53821	defect
5	219	atrioventricular septal defect
6	12591	atrioventricular
7	29993	canal
8	53821	defect
9	79	atrioventricular canal defect
10	26	AVSD
11	5223	endocardial
12	1225	cushion
13	53821	defect
14	213	endocardial cushion defect
15	673	#1 or #5 or #9 or #10 or #14
1	8623465	PY <= "1995"
17	630	#15 and (PY <= "1995")
18	471295	explode "Infant"/ all subheadings
19	259933	explode "Infant-Newborn"/ all subheadings
20	471295	#18 or #19
21	340	#17 and #20
22	17629	explode "Heart-Defects-Congenital"/ surgery
23	193	#21 and #22
24	6663681	LA = "ENGLISH"
* 25	134	#23 and (LA = "ENGLISH")

Appendix D: Medline Silverplatter search strategy for total anomalous pulmonary venous drainage

No.	Records	Request
1	361730	total
2	8827	anomalous
3	223516	pulmonary
4	70220	venous
5	33883	drainage
6	216	total anomalous pulmonary venous drainage
7	8827	anomalous
8	223516	pulmonary
9	70220	venous
10	33883	drainage
11	380	anomalous pulmonary venous drainage
12	45	TAPVD
13	388	#6 or #11 or #12
14	8623465	PY <= "1995"
15	372	#13 and (PY <= "1995")
16	471295	explode "Infant"/ all subheadings
17	259933	explode "Infant-Newborn"/ all subheadings
18	471295	#16 or #17
19	213	#15 and #18
20	17629	explode "Heart-Defects-Congenital"/ surgery
21	88	#19 and #20
22	6663681	LA = "ENGLISH"
* 23	63	#21 and (LA = "ENGLISH")

Appendix E: Medline Silver platter search history for truncus arteriosus

No.	Records	Request
1	75	explode "Truncus-Arteriosus"/ all subheadings
2	1074	truncus
3	6634	arteriosus
4	759	truncus arteriosus
5	759	#1 or #4
6	8623465	PY < "1996"
7	726	#5 and (PY < "1996")
8	471295	explode "Infant"/ all subheadings
9	259933	explode "Infant-Newborn"/ all subheadings
10	471295	#8 or #9
11	409	#7 and #10
12	17629	explode "Heart-Defects-Congenital"/ surgery
13	204	#11 and #12
14	6663681	LA = "ENGLISH"
* 15	151	#13 and (LA = "ENGLISH")

Appendix F: Medline Silverplatter search strategy for the Fontan procedure

No.	Records	Request
1	164	explode "Fontan-Procedure"/ all subheadings
2	1398	fontan
3	1398	fontan
4	159874	procedure
5	499	fontan procedure
6	333	univentricular
7	47872	heart
8	212	univentricular heart
9	361730	total
10	247	cavopulmonary
11	17832	connection
12	75	total cavopulmonary connection
13	361730	total
14	247	cavopulmonary
15	23897	anastomosis
16	16	total cavopulmonary anastomosis
17	33	TCPC
18	1590	#1 or #2 or #5 or #8 or #12 or #16 or #17
19	8623465	PY < "1996"
20	1469	#18 and (PY < "1996")
21	1381721	explode "Child"/ all subheadings
22	471295	explode "Infant"/ all subheadings
23	1381721	#21 or #22
24	968	#20 and #23
25	17629	explode "Heart-Defects-Congenital"/ surgery
26	511	#24 and #25
27	6663681	LA = "ENGLISH"
*28	416	#26 and (LA = "ENGLISH")

Appendix G: Data extraction sheet

Operation code

Study id

Publication year

Duration of study (months)

Year study began

Country of study

Centre of study

Study type

Number of centres

Number of cases

Complexity

Mean weight (kg)

Mean age (days or months)

Are aims of the study are clear?

Is case-definition clear?

Are patients in case series consecutive?

Use of confidence intervals? (estimate of random variability)

Is there stratification by comorbidity ?

Is 30-day mortality defined?

Appendix H: References included in these analyses

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Appendix I: Diagrammatic representations of congenital cardiac defects and normal circulation
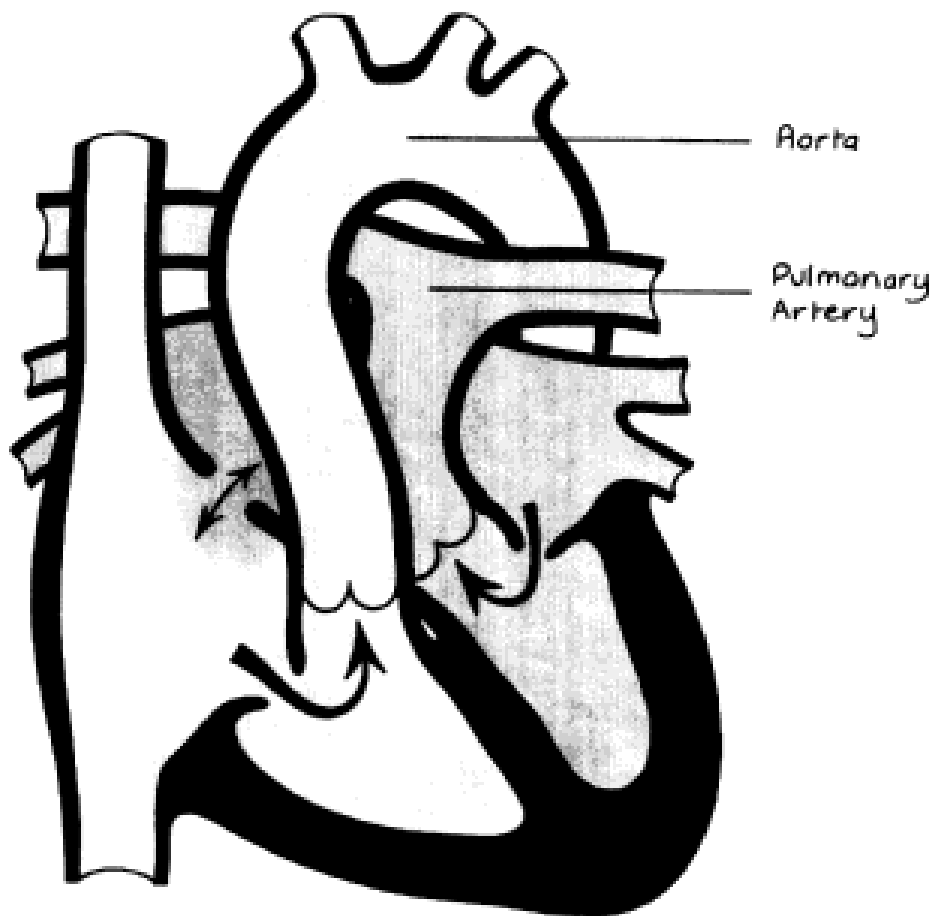
Plate 1: Normal circulation
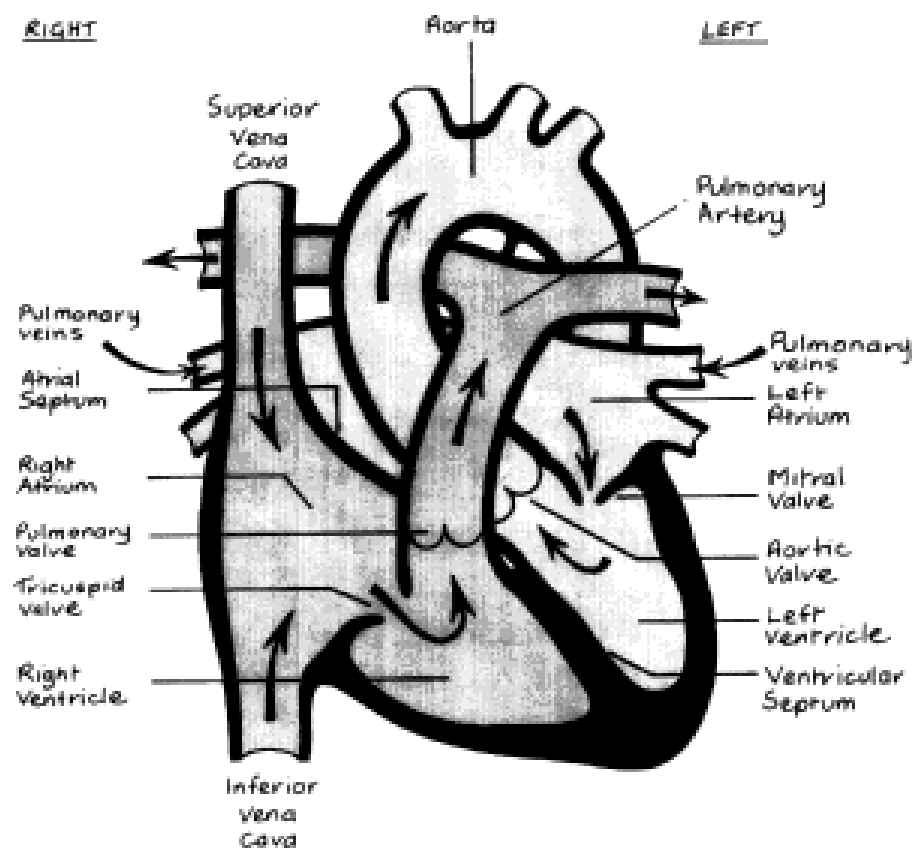
NORMAL CIRCULATION
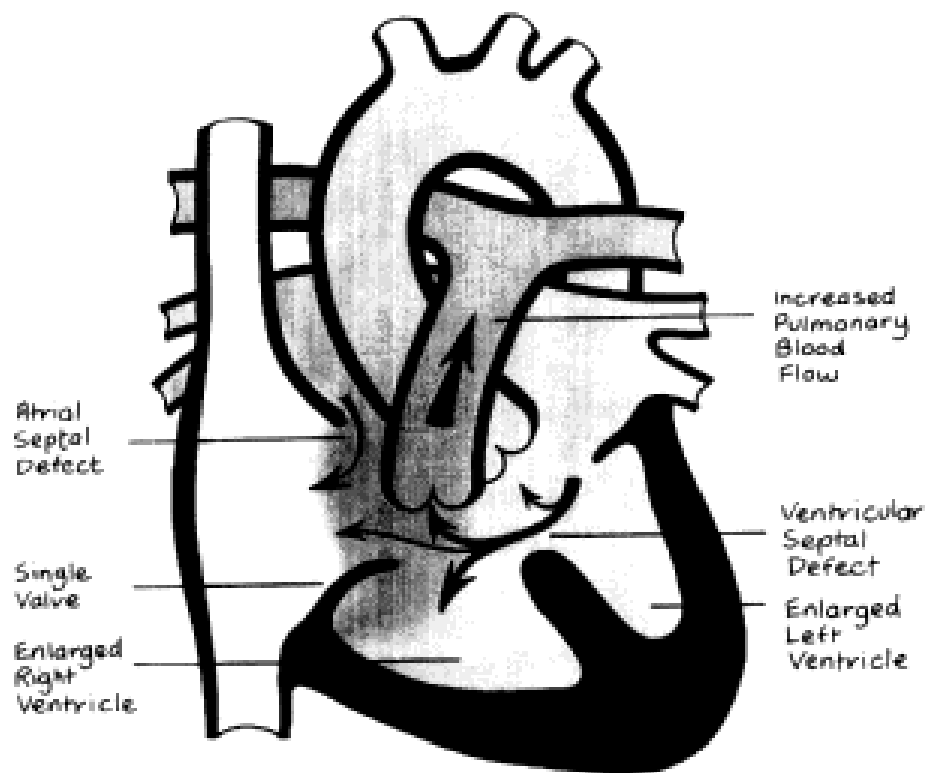
Plate 2: Simple transposition of the great arteries

ES 0001 0012

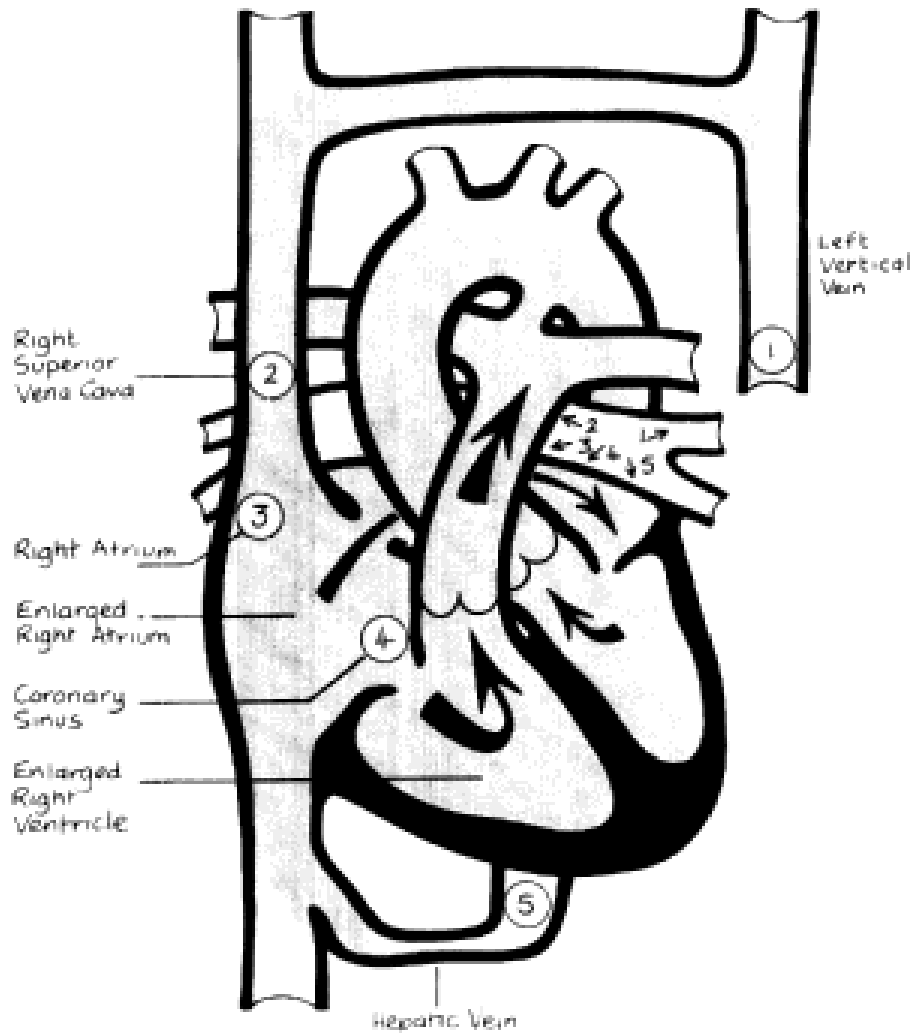SIMPLE TRANSPOSITION

Plate 3: Complete atrioventricular septal defect

COMPLETE ATRIO-VENTRICULAR SEPTAL DEFECT

Plate 4: Total anomalous pulmonary venous drainage

ES 0001 0017

Left Vertical Vein

Right Superior Vena Cava — ②

③

Right Atrium —

Enlarged Right Atrium — ④

Coronary Sinus —

Enlarged Right Ventricle —

⑤

Hepatic Vein

TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Plate 5: Truncus Arteriosus

TRUNCUS ARTERIOSUS
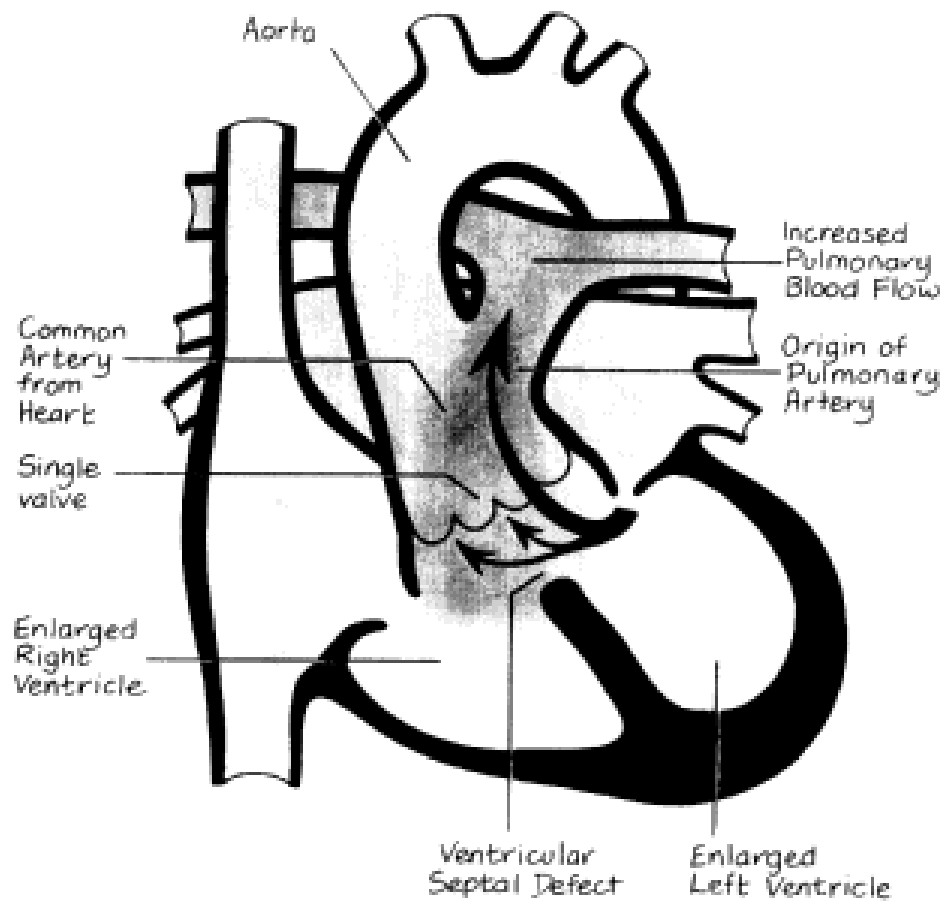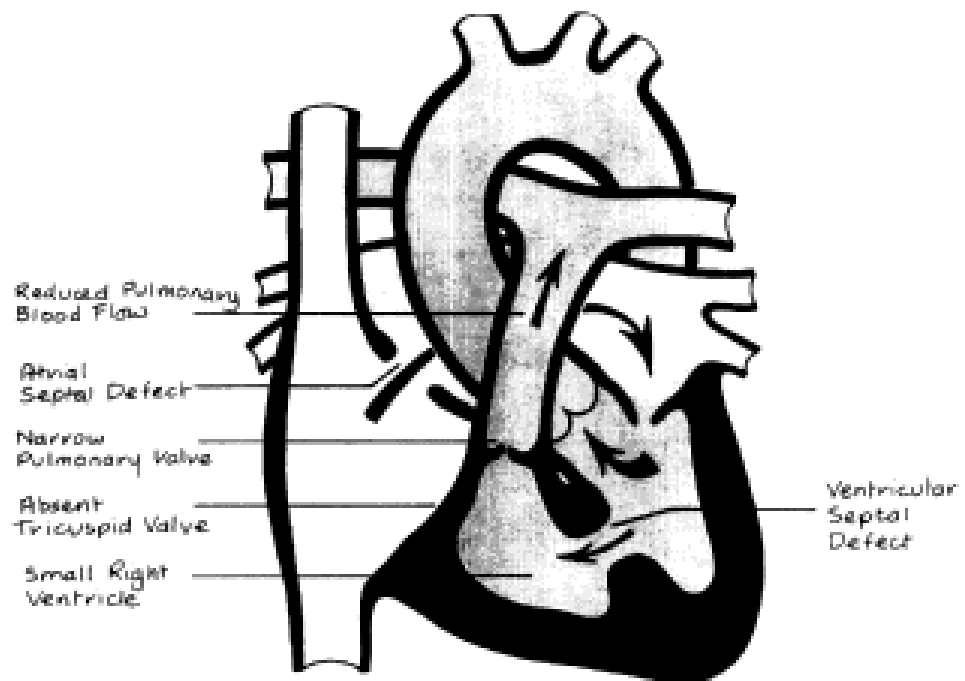
Plate 6: Univentricular heart defects: Tricuspid atresia

ES 0001 0015

TRUCUSPID ATRESIA

Plate 7: Univentricular heart defects: Hypoplastic left heart

ES 0001 0018

HYPOPLASTIC LEFT HEART