European Journal of Epidemiology (2005) 20: 549–557
DOI 10.1007/s10654-005-4264-9

NEW STUDY

CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: Rationale, design, and first results

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Accepted in revised form 22 March 2005

Abstract. *Introduction*: Survival of patients with congenital heart disease has dramatically improved after surgical repair became available 40 years ago. Instead of a mortality of 85% during childhood following the natural course, over 85% of these infants are now expected to reach adulthood. However, data on long-term outcome is scarce due to the lack of large, national registries. Moreover, little is known about the genetic basis of congenital heart defects. In 2000, the Interuniversity Cardiology Institute of the Netherlands and the Netherlands Heart Foundation have taken the initiative to develop a national registry and DNA-bank of patients with congenital heart disease in the Netherlands named CONCOR. *Objectives*: The aims of the CONCOR project are to facilitate investigation of the prevalence and long-term outcome of specific congenital heart defects and their treatment, to develop an efficient organisational structure for the improvement of healthcare for patients with congenital heart disease, and to allow investigation of the molecular basis of congenital heart defects. *Methods*: After informed consent, research nurses enter data of participating patients into the CONCOR database using a web application. Data is transferred over the Internet via a secure connection. About 20 ml blood is withdrawn from the patient, and the DNA is isolated and stored. From each participating patient family history on congenital heart disease is obtained. *Results*: Within two and a half years more than 4200 patients have agreed to participate. More than 99% of the patients that were asked have given their consent to participate in CONCOR. From 60% of these patients DNA has already been obtained. Mean age of the patients included is 34 years; more than 85% of the patients are younger than 45 years. Late complications occur frequently and the incidence increases with advancing age. 18% of the patients are known with supraventricular or ventricular arrhythmias. 2% of the included patients suffered a cerebrovascular accident, 139 (3%) had endocarditis. 6% of the patients has pulmonary hypertension or Eisenmenger syndrome. More than 15% of the patients reported an affected family member with congenital heart disease in the first, second, or third degree. 6% has an affected first-degree relative, and 4% a second-degree relative. Already 10 research projects have started using the CONCOR data and DNA. *Conclusion*: The population of patients with congenital heart disease is young and rapidly growing. Late complications occur frequently and the incidence increases with advances age. The CONCOR registry and DNA-bank facilitates research on prevalence and long-term outcome and allows investigation of the molecular basis of congenital heart disease.

Key words: Registry, Genetics, Adult congenital heart disease

Introduction

Multiple epidemiologic studies on congenital heart disease have been published. These studies vary substantially in design and use different pathologic descriptions, complicating their interpretation. In addition, most predate the use of echocardiography, so that misdiagnosis of complex defects and underdiagnosis of mild defects most likely occurred. The incidence of congenital heart defects, as reported in the literature, is 6–8 per 1000 live births [1, 2]. Botto et al. recently suggested that the prevalence of congenital heart disease is increasing because their findings could not be solely attributed to improved case ascertainment and reporting. Furthermore they found racial variations in the occurrence of several congenital heart defects [3]. However, other authors did not find changes in incidence in different

countries, races or times [2, 4]. Although the exact incidence of congenital heart disease in the Netherlands is also unknown, it is estimated that every year 1500 children with congenital heart disease are born in the Netherlands. It is estimated that – at this moment – the number of adults with congenital heart disease in the Netherlands could be around 20,000 – 25,000. This number plus an additional 25,000 pediatric patients gives an estimated total of 50,000 patients with congenital heart disease in the Netherlands.

Exact data on long-term outcome in this population are not available due to the fact that a large, national registry is lacking. Several national reports have stressed the importance of the development of a national registry of these patients in the Netherlands to improve knowledge and experience in the care of patients with congenital heart disease. In the recent reports of the British Cardiac Society Working Party and the Task Force of the European Society of Cardiology on grown-up congenital heart disease the development of such a national registry was also considered "a major priority" [5, 6].

In the last few years the genetic aspects of congenital heart disease have increasingly become a field of interest for research [7]. So far, little is known about the genetic, molecular basis of congenital heart disease but more and more genes are identified to play a role in the development of the heart. Moreover, it also has become clear that children of patients with congenital heart disease have a higher risk of congenital heart defects than children of normal individuals [8]. These facts necessitate augmentation of genetic research in patients with congenital heart disease.

In 2000, the Interuniversity Cardiology Institute of the Netherlands (ICIN) and the Netherlands Heart Foundation took the initiative for the development of a national registry and DNA-bank of patients with congenital heart disease, named CONCOR ("CONgenital CORvitia"). The aims of the CONCOR project are: to facilitate investigation of prevalence and long-term outcome of specific congenital heart defects and their treatment, to develop an efficient organisational structure for the improvement of healthcare for patients with congenital heart disease, and to allow investigation of the molecular basis of congenital heart defects. Purpose of this paper is to describe the design, methodology and present status of the CONCOR registry and DNA-bank.

Methods

Study population and selection procedure

All patients with structural congenital heart defects or Marfan syndrome are eligible candidates for inclusion in CONCOR. By convention, structural congenital heart defects also include bicuspid aortic valve, mitral valve prolaps and congenital regurgitant and/or stenotic valves. Patients with cardiomyopathies (i.e. arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, dilated cardiomyopathy) and inherited diseases leading to genetically determined cardiac arrhythmias and sudden death (i.e. long QT syndrome, Brugada syndrome) are excluded from participation. For the diagnosis of Marfan syndrome the criteria of the Ghent nosology need to be satisfied [9].

Participants and organisation

The CONCOR project has been initiated by the Interuniversity Cardiology Institute of the Netherlands (ICIN) and the Netherlands Heart Foundation in collaboration with the Departments of Cardiology of all 8 University Medical Centers in the Netherlands. More than 20 large non-university hospitals have joined the CONCOR project and their number is steadily increasing. In the last trimester of 2004 the pediatric cardiologists have started a pilot-phase in which their participation is carefully prepared. They are expected to include their first patients in the first months of 2005.

The CONCOR organisation consists of a Steering committee and Project group. The Steering committee consists of representatives of the Departments of Cardiology and Pediatric Cardiology of the participating centers, the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and 2 independent experts in medical genetics. The project group consists of the project manager, an IT manager, research-fellow and 4 research nurses. The Steering Committee supervises the CONCOR project. Every 3 months the project group reports to the Steering Committee on progress, plans and methodological issues. The project group is responsible for inclusion of patients, acquisition of new hospitals, public relations and project documentation.

Ethics and legal status

The ethics review boards of all participating medical centers have approved the CONCOR project. The methodology and privacy regulations are in accordance with the Dutch and European Privacy Protection Laws, and have been approved by the Ministery of Justice in the Netherlands.

Inclusion procedure

Patients are asked to participate by their cardiologist or one of the 4 CONCOR research nurses during their visit to the outpatient clinic. Patients are informed about aims and procedures of the CONCOR

project, and that no individual, future results from DNA analyses will be reported to them. After consent no further action on their part is needed. 20 cc EDTA of venous blood is drawn from patients. Participation in only the CONCOR-registry is possible: blood withdrawal is not mandatory to participate in CONCOR.

Data-collection, storage and protection

Trained research nurses enter the clinical data of participating patients in the CONCOR database. Patients are labelled with a unique CONCOR-number. For each patient, identifying data, clinical events (diagnoses and interventions) and family history for congenital heart disease are registered. The clinical events are coded using the European Pediatric Cardiac Code Short List coding scheme, a coding system developed by the Association for European Paediatric Cardiology [10]. In every patient one diagnosis is considered the main event and the other diagnoses and interventions are considered subevents. This allows identification of all patients with their main congenital defect. For each patient the familial history is obtained (the number, gender and degree of affected family members with congenital heart disease).

All data that are collected are stored in one central relational database (Microsoft SQL-server) using the ProMISe system (http://promise.clinicalresearch.nl). The current server is a Windows 2000 advanced server with 8 GB memory, 8 CPU's and 450 GB hard disk space. ProMISe ("Project Manager Internet Server") has been developed and is maintained at the department of Medical Statistics of the Leiden University Medical Center. ProMISe is a generic Internet based application for the Design, Maintenance and Use of (clinical) data management projects, and is presently used by a number of other registries, such as the European Blood and Marrow Transplantation (EBMT) Group. Both the design and data handling for a project is integrated into the web application, allowing the designer to change any aspect of the project while in production. No additional software is required.

A large number of security measures have been taken to ensure the integrity of the data. The ProMISe server is located in one of the dedicated server rooms of the Leiden University Medical Center, configured in a dedicated 'demilitarized zone', and protected using 2 separate firewalls. The only access to the server that is allowed is through the https and ftp protocol (the latter only for static web pages). Users (or the designer or administrator of the project) log on to their own project with a standard web browser (Microsoft Internet Explorer) over a secure connection from any location on the Internet, using individual username-password combinations. The passwords that can be used must adhere to the specific Microsoft recommendations and are stored encrypted. All activities and modifications are logged on IP and user level.

Initially, an independent software company has reviewed the design of ProMISe (on request by the EBMT which triggered the creation of ProMISe) by assessing the basic design of ProMISe, its concepts and its security implementation. It qualified the design and first version as "state of the art" and gave a positive advice to the EBMT Board to use ProMISe as its data management system for all transplantations in Europe. ProMISe currently runs a variety of national and international clinical studies and registrations in haematology, cardiology, orthopaedics, oncology, neurosurgery, paediatrics and neurology.

Data analysis, reporting, quality control

The ProMISe system is an open structure that allows (and supports) the export of the data dictionary and the data itself to any other format, such as Microsoft Access.

Various queries on the CONCOR database have been designed to create reports based on the content of the registry. Participating centers receive regular reports based on these queries on the progress in their center and on a national basis. Furthermore, monthly reports are published in the Netherlands Heart Journal based on the total data-collection. Centers are regularly visited to discuss progress, local procedures, user's satisfaction and possible complaints. A printed report of the data entry is kept in the patient's records allowing the cardiologist to easily review the patient's medical history and correct it where necessary. To assure the quality of the data in the CONCOR registry, a large number of quality assurance measures have been implemented.

For quality assurance, a number of additional queries are carried out monthly to identify possible errors or inconsistencies. Some of the items that are checked are:

- Incomplete patient records
- Duplicate (patient) entries
- Correctness of patient-ID and birth-date
- Agreement between the information in the DNA-lab database and the CONCOR database
- Overall consistency.

In addition, patient records are selected at random regularly, and are checked by a trained physician (with special emphasis on the correct coding of the events).

DNA-isolation and storage

After withdrawal the blood is cooled at a temperature of 4° Celsius and labelled with the unique corresponding CONCOR-number. Subsequently, it is either sent or taken by the nurse to the DNA diagnostics laboratory of the Academic Medical Center in

Amsterdam. Upon arrival at the laboratory the 20 ml EDTA blood is stored at 4 °C. Within 24 h DNA is extracted from 10 ml of this sample using the PUREGENE DNA extraction method of GENTRA (http://www.gentra.com/pdf/PL-0113.pdf). The DNA is subsequently stored at 4 °C. From the remaining 10 ml blood, lymphocytes are isolated and stored at −80 °C for later DNA isolation.

Data and DNA delivery

Researchers with a request for CONCOR data and DNA can submit their research proposal and DNA-request form (when applicable) via the CONCOR website. In principle any researcher with a specific scientific question can apply for data (and DNA) from the CONCOR database. The project group sends this request to the members of the Steering Committee for review. This review is carried out within maximal two weeks. If the aims and procedures as described in the privacy regulations are met, the proposal is approved by the Steering Committee. The Steering Committee will then give a positive advice to the Interuniversity Cardiology Institute of the Netherlands. The ICIN notifies the researcher that the data and DNA can be obtained, and the project group is requested to arrange this delivery. The entire procedure until delivery takes less than 3 weeks.

Results

Inclusion

The inclusion has started in November 2001. Presently, 21 hospitals are actively participating in the CONCOR project (8 University Hospitals, and 13 non-University Hospitals). More than 99% of the patients that were asked to participate have given their permission for registration. 99% of these patients have given their consent to also participate in the CONCOR DNA-bank. Currently, more than 4000 adult patients with congenital heart disease are registered (September 29, 2004: N = 4252). From 62% of these patients DNA has already been obtained during their visit to the outpatient clinic or during home visits by the research nurses. The remaining patients will be contacted at a later stage.

In addition, patients also contact the CONCOR projectgroup directly. These patients are informed about the CONCOR registration project via e.g. articles in non-scientific journals, radio/TV and through various patient organisations. The CONCOR research nurses then get in touch with these patients to enroll them in the CONCOR registry. The hospitals where these patients are under treatment are registered as 'passively participating hospitals', resulting in a total number of participating hospitals of 54. Presently, about 300 patients have applied for registration this way, and have been included or will be included shortly (on a total of 4252 included patients).

Clinical characteristics of the included population

52% of patients are male, 48% female. Mean age is 34.0 ± 12.9 year (range: 16–83 year). More than 85% of the included patients are younger than 45 years (See Figure 1).

Figure 2 shows the distribution of main diagnoses in the total group of included patients. Tetralogy of Fallot is the most prevalent main diagnosis (N = 601, 14.1%) followed by aortic coarctation (N = 442, 10.4%), Ventricular Septal Defects (VSD) (N = 433, 10.2%), Atrial Septal Defects (ASD) (N = 379, 8.9%) and aortic valvar stenosis (N = 356, 8.4%) (see Figure 2). Figure 3 shows the 7 most prevalent main diagnoses in both the academic hospitals and non-academic hospitals. The figure shows that patients who are under treatment in the non-academic hospitals mostly have 'simple' lesions (ASD, VSD), while patients in the academic centers have more complicated lesions. Corrective or palliative surgery has been performed in 76% of the patients. Many of these patients required more than 1 intervention: 53% has had 1 intervention, 25% 2 interventions, 22% 3 or more interventions (Figure 4).

Late complications

Long-term complications occur frequently and are a concern in many patients. 18% of the patients are known with supraventricular or ventricular arrhythmias. The prevalence of arrhythmias by age is given in figure 5. Among all patients older than 50 years the prevalence is 38%. Figure 6 shows the prevalence of supraventricular and ventricular arrhythmias in several main diagnosis groups. 18% of the patients with Tetralogy of Fallot and more than 50% of the patients with a Fontan circulation are known with supraventricular arrhythmias. 2% of the included patients suffered a cerebrovascular accident, 139 (3%) had endocarditis. 6% of the patients (227) had pulmonary

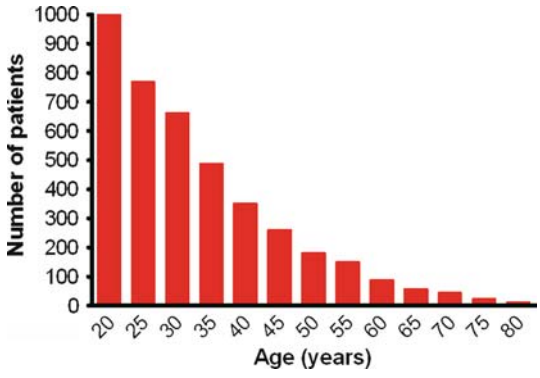

Figure 1. Age distribution.

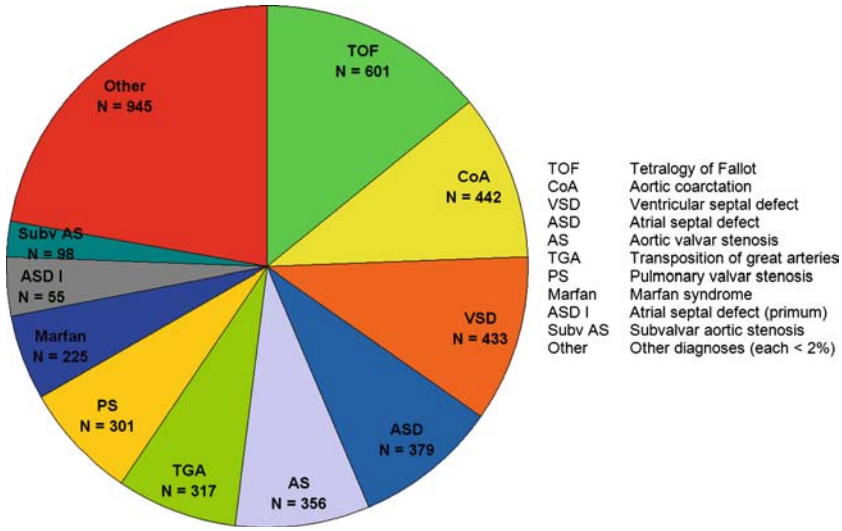

Figure 2. Distribution of main diagnoses.

hypertension (peak systolic pulmonary arterial pressure > 35 mmHg at Doppler-echocardiography) or Eisenmenger syndrome. Figure 7 shows the prevalence of pulmonary hypertension in several main diagnosis groups. 42% of the patients with atrioventricular septal defect, and 32% of the patients with double outlet right ventricle (DORV) have pulmonary hypertension or Eisenmenger syndrome.

Family history

More than 15% of the patients reported an affected family member with congenital heart disease in the first, second, or third degree. 6% has an affected first-degree relative, and 4% a second-degree relative.

Research proposals

Already 10 research proposals have been approved within the first three years of the CONCOR project. Three projects are investigating long-term outcome in specific groups of patients with congenital heart disease. The other projects are investigating the molecular basis of congenital heart defects using DNA from the CONCOR DNA-bank.

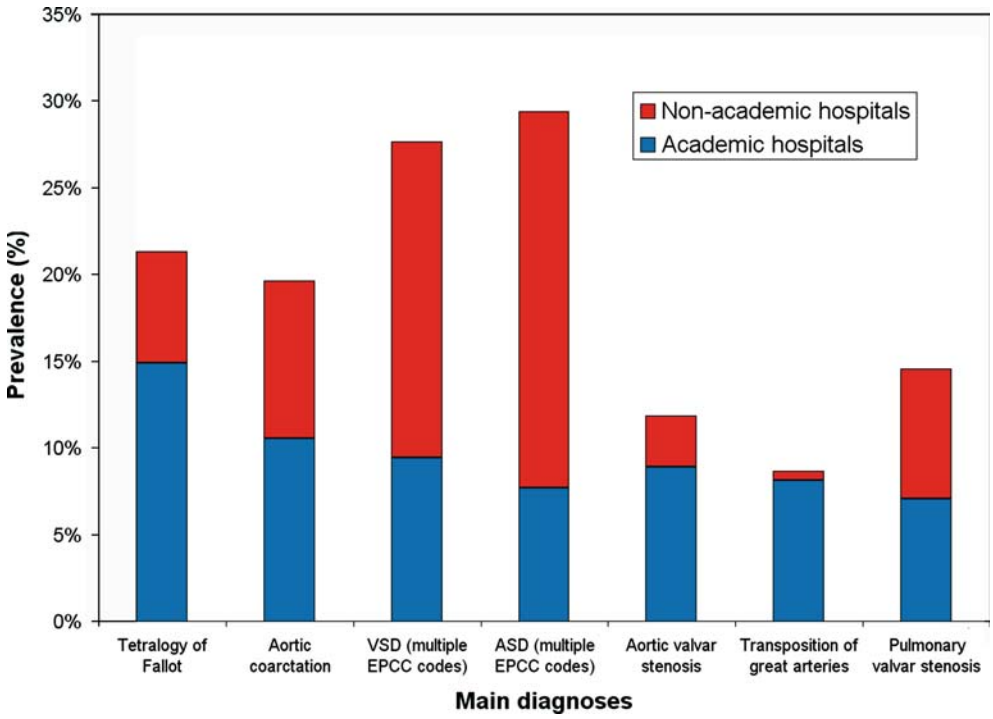

Figure 3. Most prevalent main diagnoses in patients from academic and from non-academic hospitals.

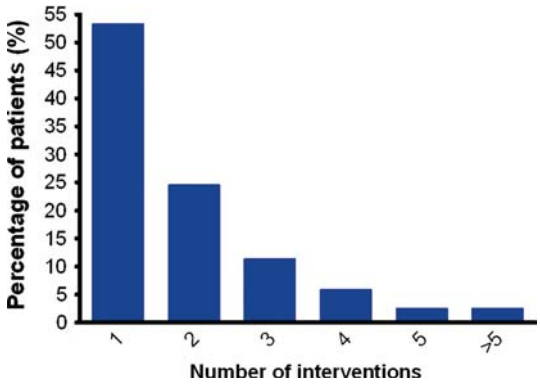

Figure 4. Distribution of the number of interventions per patient.

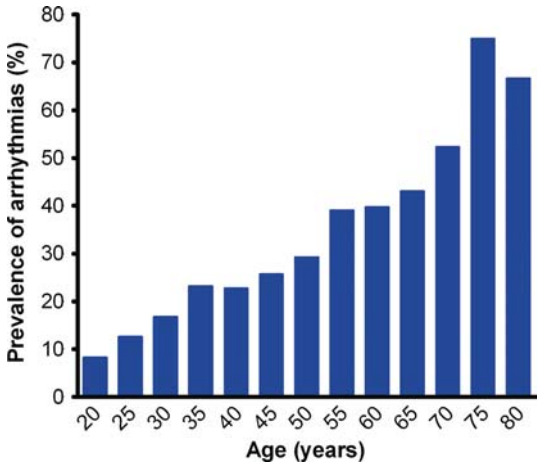

Figure 5. Prevalence of arrhythmias versus age.

Discussion

CONCOR, the national registry and DNA-bank of patients with congenital heart disease facilitates research on long-term outcome and allows investigation of the molecular basis of congenital heart defects. The ultimate aim is to establish a complete registry of all patients with congenital heart disease in the Netherlands. The first two years of the CONCOR project have been successful considering the number of patients included and the number of research projects that have been started using CONCOR data and DNA. National registries on congenital heart disease are of crucial importance to investigate prevalence and long-term outcome and to improve health care for the rapidly growing population of patients with congenital heart disease.

In the 1960's, before the development of cardiac surgery with cardiopulmonary bypass, about 50% of the children with congenital heart disease requiring therapy died within the first year of life and less than 15% reached adulthood. Especially patients with transposition of the great arteries had a poor survival: 90% of the patients died in the first month of life and less than 1% reached adult age. Only 10% of the patients with Tetralogy of Fallot survived until adult age. Major developments in medical care have radically changed the prognosis of patients with congenital heart disease. More accurate diagnosis, improved surgical skills and postoperative care have led to a decline in peri-operative mortality and provided treatment options for complex congenital cardiac defects formerly considered inoperable. Instead

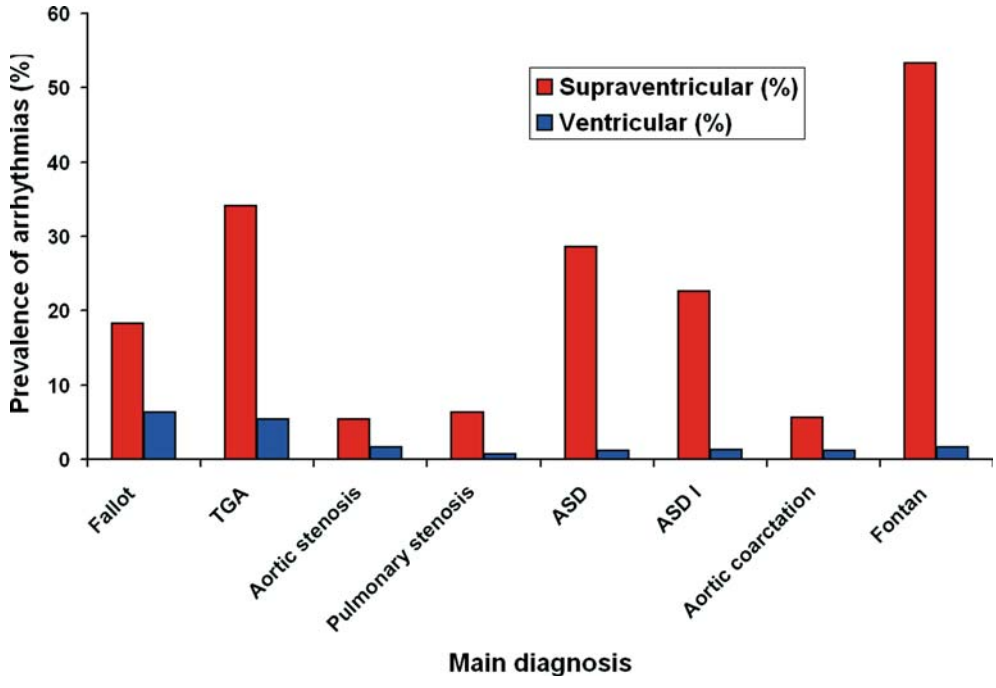

Figure 6. Prevalence of arrhythmias in several main diagnosis groups.

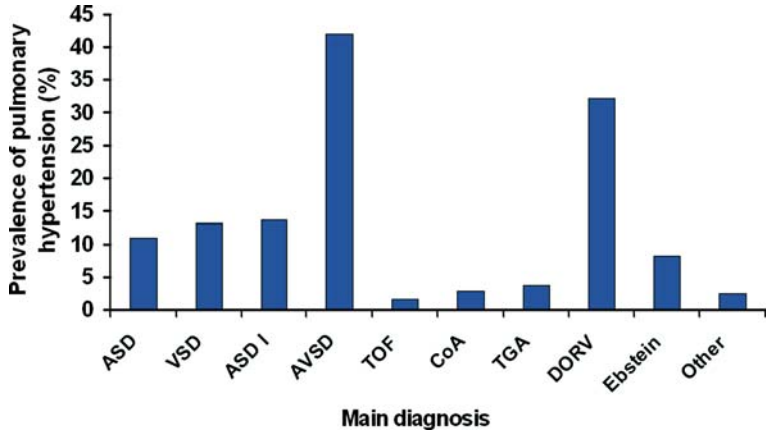

Figure 7. Prevalence of pulmonary hypertension in several main diagnosis groups.

of a mortality of 85% during childhood following the natural course, over 85% of these infants are now expected to reach adulthood [11]. These successes have led to a new patient population consisting of young adults with a surgically corrected heart defect. This is illustrated by the two-years results of the CONCOR-project, which show that 86% of the patients in the CONCOR registry are between 20 and 40 years of age and 75% of the patients had previous surgery.

Data on long-term follow up are lacking but it has become increasingly clear that, although the survival results are gratifying, complete cure is seldom achieved. Except for a patent arterial duct that has been closed either spontanously or surgically, all patients with congenital heart disease have more or less residual abnormalities after surgical repair. Less than 10 percent of these adults patients with congenital heart disease is significantly handicapped, but in the majority of patients significant long-term complications occur frequently and often require indefinite follow up [6,7]. The most common complications in adult patients with congenital heart disease are: arrhythmia, heart failure (often of the right ventricle), endocarditis, cardiac conduit obstructions, valve regurgitation and pulmonary hypertension. The results of the CONCOR project also show a high prevalence of late complications in the entire population. For example, the preliminary results of the CONCOR registry show a significant prevalence of supraventricular and ventricular arrhythmia in the entire population. The prevalence of atrial arrhythmias in the general population has been reported to be below 1% in subjects up to 60 years of age, rising to around 10% in subjects above 70 years of age [12,13]. Since the prevalence of ventricular arrhythmia in the general population is negligible, this roughly represents the prevalence of all arrhythmia, and is clearly much lower than in the CONCOR population, As the population of patients with congenital heart disease is growing and getting older, the frequency of hospital admissions for treatment of these arrhythmias is likely to increase. Not only ventricular arrhythmias but also atrial tachycardia (atrial flutter) may lead to sudden death in this population due to the disturbance of the subtle hemodynamic balance in patients with ventricular dysfunction. Atrial flutter may be the first sign of cardiac conduit obstruction, so an examination with echocardiography or magnetic resonance imaging (MRI) is indicated in these cases. These difficulties are an example and imply follow up and treatment of this patient population in a centre with specific knowledge and expertise in the field of congenital heart disease.

The cause of congenital heart defects is unknown. Both environmental and genetic factors have been implicated. The genetic causes of multiple vascular, myopathic and arrhythmogenic cardiovascular disorders have been identified because many of these disorders are familial. Large families with multiple affected family members allow for parametric linkage analyses that identify disease loci and disease genes. In contrast, identification of specific genetic causes for intracardiac malformations has been difficult because large families with multiple affected members are uncommon [4]. Congenital heart defects are often considered to be sporadic events, but evidence suggests that some cases result from inherited, genetic traits. Several studies have demonstrated that children of patients with congenital heart disease have a higher risk of congenital heart defects than children of normal individuals [8, 14]. Unfortunately, the risk of recurrence for any single family is difficult to predict given how few specific causes are presently known or can be tested. Counseling a family with one affected parent or offspring on the risk of recurrence can be challenging and still relies heavily on the general conclusions of past epidemiologic studies [4]. More than 15% of the patients in the CONCOR registry report an affected family member with congenital heart disease. 6% report an affected family member in the first degree. This is higher than the 2–4% generally considered applicable for the entire population of

patients with congenital heart disease [8]. There may be some bias caused by the fact that presently the majority of patients have been included in tertiary referral centers. Families with clustering of congenital heart disease are probably more likely to be followed in these centers. As an increasing number of non-academic hospitals is now joining the CONCOR project this figure may somewhat decrease. Nevertheless, the role of genetic defects in the development of these malformations appears to be more important than previously thought.

Registration and collection of DNA of patients with congenital heart disease are important tools to facilitate research on long-term outcome and to allow investigation of the molecular basis of congenital heart defects. The availability of a national registry is mandatory for scientific research and management [5]. Within just two years the CONCOR project has become the third largest registry on congenital heart disease in the world [15]. The combination of this large registry and the DNA-bank makes the CONCOR project unique in the world. Probably the most successful result of the CONCOR-project has been the number of research projects that have started and that are now using CONCOR data and DNA. CONCOR has been a strong stimulant for research on congenital heart disease in the Netherlands. As CONCOR is likely to grow the coming years, the registry and DNA-bank will gain further importance. The participation of the pediatric cardiologists will give more specific information on the incidence and prevalence of congenital heart disease in the Netherlands. Moreover, the coming years CONCOR will allow investigation of follow-up in specific, large cohorts of patients with congenital heart disease with the potential to improve healthcare for this special patient population.

Acknowledgments

This research was supported in part by a grant from the Netherlands Heart Foundation (NHS/2001T501) and by a grant from the Interuniversity Cardiology Institute of the Netherlands. JV is a clinical researcher for the Interuniversity Cardiology Institute of the Netherlands (ICIN).

Conclusion

The two-year results of the CONCOR-project show that the population of patients with congenital heart disease is young and rapidly growing. Late complications occur frequently and the incidence increases with advanced age. As an increasing number of patients now reaches adulthood and have children, the role of genetic defects in the development of these malformations seems to be more important than previously thought. The CONCOR registry and DNA-bank facilitate research on long-term outcome and allows investigation of the molecular basis of congenital heart disease.

References

1. Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, et al. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. Am J Epidemiol 1985; 121(1): 31–36.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002; 39(12): 1890–1900.
3. Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. Pediatrics 2001; 107(3): E32.
4. Goldmuntz E. The epidemiology and genetics of congenital heart disease. Clin Perinatol 2001; 28(1): 1–10.
5. Grown-up congenital heart (GUCH) disease. current needs and provision of service for adolescents and adults with congenital heart disease in the UK. Heart 2002; 88(Suppl 1): i1–14.
6. Deanfield J, Thaulow E, Warnes C, Webb G, Kolbel F, Hoffman A, et al. Management of grown up congenital heart disease. Eur Heart J 2003; 24(11): 1035–1084.
7. Perloff JK, Warnes CA. Challenges posed by adults with repaired congenital heart disease. Circulation 2001; 103(21): 2637–2643.
8. Burn J, Brennan P, Little J, Holloway S, Coffey R, Somerville J, et al. Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. Lancet 1998; 351(9099): 311–316.
9. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996; 62(4): 417–426.
10. Franklin RC, Anderson RH, Daniels O, Elliott M, Gewillig MH, Ghisla R, et al. Report of the Coding Committee of the Association for European Paediatric Cardiology. Cardiol Young 2000; 10(Suppl 1): 1–26.
11. Perloff JK. Congenital heart disease in adults. A new cardiovascular subspecialty. Circulation 1991; 84(5): 1881–1890.
12. Camm AJ, Obel OA. Epidemiology and mechanism of atrial fibrillation and atrial flutter. Am J Cardiol 1996; 78(8A): 3–11.
13. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82(8A): 2N–9N.
14. Nora JJ, Nora AH. Update on counseling the family with a first-degree relative with a congenital heart defect. Am J Med Genet 1988; 29(1): 137–142.
15. Niwa K, Perloff JK, Webb GD, Murphy D, Liberthson R, Warnes CA, et al. Survey of specialized tertiary care facilities for adults with congenital heart disease. Int J Cardiol 2004; 96(2): 211–216.

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