Congenital Heart Disease (CHD) is the most frequently occurring congenital disorder. A few decades ago, only a minority of patients with moderate and severe CHD reached adulthood. The introduction of cardiopulmonary bypass in the 1950s enabled large-scale intracardiac repair in these patients, with subsequent dramatic improvement of long-term survival. The ongoing search for progress and the growing understanding of the cardiovascular system and its pathophysiology refined all aspects of care for these patients. As a consequence, survival further increased over the past decades, and a new group of patients, those who survived congenital heart disease into adulthood, emerged. However, a large range of complications raised at the horizon as arrhythmias, endocarditis, pulmonary hypertension, and heart failure, and the need for additional treatment became clear. Technical solutions were sought in perfection and creation of new surgical techniques by developing catheter-based interventions, with elimination of open heart surgery and new electronic devices enabling, for example, multisite pacing and implantation of internal cardiac defibrillators to prevent sudden death. Over time, many pharmaceutical studies were conducted, changing clinical treatment slowly toward evidence-based care, although results were often limited by low numbers and clinical heterogeneity. More attention has been given to secondary issues like sports participation, pregnancy, work, and social-related difficulties. The relevance of these issues was already recognized in the 1970s when the need for specialized centers with multidisciplinary teams was proclaimed. Finally, research has become incorporated in care. Results of intervention studies and registries increased the knowledge on epidemiology of adults with congenital heart disease and their complications during life, and at the end, several guidelines became easily accessible, guiding physicians to deliver care appropriately. Over the past decades, the landscape of adult congenital heart disease has changed dramatically, which has to be continued in the future. (Circ Res. 2017;120:908-922. DOI: 10.1161/CIRCRESAHA.116.309302.)

Key Words: congenital heart disease ■ epidemiology ■ morbidity ■ mortality

Congenital heart disease (CHD) is the most frequently occurring congenital disorder affecting ≈0.8% of live births. Thanks to great efforts and technical improvements, including the development of cardiopulmonary bypass in the 1950s, large-scale repair in these patients became possible, with subsequent dramatic reduction in morbidity and mortality. The ongoing search for progress and the growing understanding of the cardiovascular system and its pathophysiology refined all aspects of care for these patients. As a consequence, survival further increased over the past decades, and a new group of patients, those who survived congenital heart disease into adulthood, emerged. However, a large range of complications raised at the horizon as arrhythmias, endocarditis, pulmonary hypertension, and heart failure, and the need for additional treatment became clear. Technical solutions were sought in perfection and creation of new surgical techniques by developing catheter-based interventions, with elimination of open heart surgery and new electronic devices enabling, for example, multisite pacing and implantation of internal cardiac defibrillators to prevent sudden death. Over time, many pharmaceutical studies were conducted, changing clinical treatment slowly toward evidence-based care, although results were often limited by low numbers and clinical heterogeneity. More attention has been given to secondary issues like sports participation, pregnancy, work, and social-related difficulties. The relevance of these issues was already recognized in the 1970s when the need for specialized centers with multidisciplinary teams was proclaimed. Finally, research has become incorporated in care. Results of intervention studies and registries increased the knowledge on epidemiology of adults with congenital heart disease and their complications during life, and at the end, several guidelines became easily accessible, guiding physicians to deliver care appropriately. Over the past decades, the landscape of adult congenital heart disease has changed dramatically, which has to be continued in the future. (Circ Res. 2017;120:908-922. DOI: 10.1161/CIRCRESAHA.116.309302.)

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Congenital heart disease (CHD) is the most frequently occurring congenital disorder.1 A few decades ago, only a minority of patients with moderate and severe CHD reached adulthood. The introduction of cardiopulmonary bypass in the 1950s enabled large-scale intracardiac repair in these patients, with subsequent dramatic improvement of long-term
survival. Although CHD is still the leading cause of mortality because of birth defects, survival through childhood has become possible for most patients, even for those with serious cardiac defects, such as hypoplastic left heart syndrome. The ongoing innovation in diagnosis and monitoring with advanced imaging techniques, biomarkers, and devices and with refinement of percutaneous and surgical interventions, the improved organization of care, and clinical research over the past decades have changed the landscape of adults with CHD dramatically. A new population, adult patients with CHD, has been created.

However, the clinical course of adults with CHD seems to be associated with many late sequelae. Pulmonary hypertension, endocarditis, arrhythmias, including sudden death and heart failure, are a few examples of often life-threatening complications bothering these patients frequently. A large number of patients need reoperations, with a further increase of mortality and morbidity. These complications have a large impact on the epidemiology of CHD. The current review discusses the several issues of this changing landscape of adults with CHD.

### Epidemiology

#### Prevalence

CHD is defined as a gross structural abnormality of the heart or great vessels. A well-organized and useful classification scheme, adapted in 2001, is being used nowadays to classify patients into CHD of great complexity, CHD of moderate severity, and simple CHD.

CHD is the most frequently occurring congenital disorder in newborns and the most frequent cause of infant death from birth defects. Birth prevalence of CHD is estimated to be 8 cases per 1000 live births (range from 3 to 10). This wide range can be explained by the challenges to estimate the exact birth prevalence because studies are hampered by several difficulties, as variations in referral and differences in access to care in population-based studies and referral bias in studies where patients are actively screened with echocardiography. An additional issue is that ≤35% of the patients are diagnosed as having a congenital heart defect after their infancy, or even in adulthood. Finally, infants who die before being diagnosed will not be included. The estimated birth prevalence for moderate and severe defects is more consistently assessed on 1.5 per 1000 live births for each group. Ethnic and geographic variations in CHD have been reported but have to overcome the aforementioned limitations and the heterogeneity among the populations under investigation. The prevalence is further influenced by the increasing detection of cardiac defects by prenatal ultrasound with subsequent termination of the pregnancy.

Nowadays, up to one third of the defects and 57% to 85% of all severe lesions are detected before the end of the pregnancy. A decline of the birth prevalence could further be because of the addition of folic acid to flour and pasta in United States and Canada and the preconceptional advice to use folic acid in Europe.

#### Etiology

The etiology of CHD is largely unknown. Only ≈15% of cases of CHD can be traced to a known cause. Several well-recognized chromosomal anomalies cause malformation syndromes that comprise 8% to 10% of CHD like Down syndrome, trisomy 13, trisomy 18, Down syndrome, Turner syndrome, and DiGeorge syndrome. Defects in single genes account for 3% to 5% of cases of CHD and are often also associated with noncardiac malformations, such as Alagille syndrome, Holt–Oram syndrome, and Noonan syndrome. The etiology of nonsyndromal CHD is less clear. About 2% of all cases of CHD can be attributed to known environmental factors. Maternal diabetes mellitus and phenylketonuria are well-accepted major risk factors for CHD. Other reported risk factors are maternal obesity, alcohol use, rubella infection, febrile illnesses, use of certain drugs, such as thalidomide and retinoic acid, and exposure to organic solvents. There are also differences in CHD presentation between men and women. In the latter, the prevalence of atrial septal defect type 2, persistent ductus arteriosus (PDA), and atrial ventricular septal defect is higher, while outflow tract defects such as transposition of the great arteries, aortic valve stenosis, coarctation, tetralogy of Fallot are more frequent in men.

#### Survival

Over the past decades, mortality has decreased significantly. A study from Norway showed an increase of survival until the age of 16 years in patients with complex CHD from 62% in 1971 to 1989 to 87% in the period 1990 to 2011 (Figure 1). Also an important reduction in reoperations in these patients was noted. Patients with simple defects were more often operated (from 12% to 34%). These epidemiological changes can be attributed to improvements in diagnostic and therapeutic interventions and will lead to sustained survival and a further increase of the population of adults with CHD. In 2000, this population was estimated to be 40 000 per 10 million inhabitants. With all improvements in care, it might be expected that the population of adults with CHD will eventually grow to an estimated population of 75 000 CHD patients per 10 million inhabitants (Figure 2).

Traditionally, Kaplan–Meier-based long-term survival from surgery of patients with CHD was presented as reflection of the effectiveness of surgical treatment. The major limitation of this approach is the lack of patients who did not receive surgery. Moreover, its validity is limited to the first 10 to 15 years after surgery, the period of childhood and early adulthood. A study on long-term survival of CHD patients in this traditional manner requests a large cohort with long survival. Still, these old cohorts do not reflect current medical care appropriately. Survival analysis with left censoring having age as...
the primary timescale has become popular to provide additional information on the long-term outcome of adults with CHD. Data from the Dutch National CONCOR registry (Congenital Heart Defects) showed that from the age of 18 years, adults with mild lesions had a median survival of 84 years, not different from that of the general population. Adults with a moderate or severe defect had a significantly lower median survival of 75 and 53 years, respectively (see Figure 3).18

Data from the same CONCOR registry revealed that two thirds of adult patients with CHD die from a cardiac cause. The most common causes of death were chronic heart failure (26%) at a median age of 51 years and sudden death (19%) at a median age of 39 years.19 Among the 23% of noncardiovascular deaths, malignancy (9%) and pneumonia (4%) were the predominant causes (Figure 4). Predictors of all-cause mortality were age, sex, CHD severity, endocarditis, supraventricular arrhythmias, ventricular arrhythmias, conduction disturbances, myocardial infarction, and pulmonary hypertension. Sex differences in outcome have been demonstrated for adult men with an atrial septal defect type 2 who appeared to have a worse survival than men in the general population. The 30-day in-hospital mortality for CHD appeared to be higher in young men than that in women of reproductive age.20 Male CHD patients also have a greater risk of endocarditis, aortic events, and indications for internal cardiac defibrillator implantation, while women tend to be more at risk of pulmonary hypertension.21 This sex disparity in survival and morbidity suggests the need for a sex-specific clinical approach toward adult patients.

During the past decades, an increasing awareness has grown about the need to deliver appropriate care in patients with end-stage CHD. There are several important end-of-life issues. How to cope with a poor prognosis when early in life a complete repair and normal lifespan was expected?22 Adequate communication with the patient and family members is essential to moderate the mourning process adequately. Crucial components in the end-of-life process are to discuss the clinical course, to limit certain interventions like resuscitation, to deactivate an internal cardiac defibrillator, and to appoint a healthcare representative.23 With the growing CHD population, the amount of patients terminally ill will increase.

Lifestyle Challenges
CHD has a large impact on working life both in men and in women, but the impact of CHD on job participation appeared to be greater in men than in women because males are more often unemployed or work part-time compared with the general population.24 Physical limitations, cognitive impairments, reduced ambition, personality traits, and even job discrimination could play a role. Attention for these issues is growing because job participation is recognized as being important for the society, as well as for the personal quality of life.25 Other restrictions in life, often experienced, are difficulties in receiving insurance and mortgage applications. These limitations seem to be unrelated to prognostic clinical factors, such as defect severity, New York Heart Association class, and left ventricular ejection fraction.26 Improvements in knowledge on CHD among the medical services of insurance companies and enhanced transparency of the insurance application process might facilitate these barriers in daily life of adult CHD (ACHD) patients.

A specific subgroup of adults with CHD are those with Down syndrome. Underdiagnosis of CHD and valvular disease is common.27 Clinical evaluation is impeded by difficulties in diagnostics, for example, different normal values of the left ventricular dimensions and different responses to exercise testing, probably related to sedentary lifestyles.28 This challenges the care of adults with an intellectual disability.

Aging of the CHD population brings new challenges. Given that many patients with CHD are prone to residual and sequela, lifelong surveillance is essential. Therefore, the first of many challenges is to optimize the transition of patients
with CHD from pediatric to adult cardiology to prevent loss to follow-up and to ensure that there are sufficient specialized adult cardiologists to take care of this expanding patient population. Another important challenge is the expansion of knowledge on long-term complications and comorbidity in these patients. Increased efforts are needed to gain further understanding on how to prevent and how to treat these complications. Furthermore, as patients reach the reproductive age, family planning becomes more important, and research on the risks and management of pregnancy should be further extended. Finally, to improve the well-being and social life of adults with CHD, efforts should be made to improve employability and insurability.22

Late Complications
As (early) surgical treatment is seldom curative, many adults with CHD have late complications, including arrhythmias, heart failure, endocarditis, pulmonary hypertension, and the need for (re)interventions.29,30 Regular follow-up of these patients should focus on early signs of these complications, early diagnosis and treatment, and education of prevention.

Heart Failure
Heart failure is common in ACHD. In Fontan patients, the prevalence of heart failure is estimated to be 10% to 20% early after completion and 40% to 50% in adulthood.31 The preceding pathophysiologic mechanisms are mainly systolic or diastolic ventricular dysfunction, valve dysfunction, and elevated pulmonary vascular resistance, all leading to fluid overload. Medical therapy is now tailored based on these pathophysiologic mechanisms, although often not completely understood, for example, renin–angiotensin–aldosterone system activation may not be the dominant pathophysiological contributor.32 The benefit of β-blocking agents is highly uncertain, especially because of the reduction in heart rate and cardiac output, which is less tolerated in patients with a single ventricle physiology. Patients with systemic right ventricles encounter similar difficulties in the treatment of heart failure symptoms. Treatment with angiotensin receptor blockers in these patients with a systemic right ventricle might offer only benefit if patients have neurohormonal activation because deterioration might also be the consequence of atrial redirection procedures, which cause failure in atrioventricular coupling, leading to an inability to increase stroke volume with exercise. Tricuspid (systemic) valve insufficiency is often also an important component in the development of heart failure. Finally, research in this area is often limited by low numbers of patients, inadequate end points such as echocardiography, and short follow-up.33 Left-sided heart failure is also very common because of the many different left-sided lesions, previous cyanosis, collateral damage during cardiac surgery, and high blood pressure. Treatment and early recognition is of utmost importance because heart failure leads to disabling symptoms and a poor prognosis as it is the most common cause of death. Nevertheless, over the past decade, the number of patients with CHD and heart failure included in clinical trials has increased, and specific guidelines have been developed.34

Arrhythmias
Arrhythmias are the most frequent long-term complications in the population with CHD and are the leading cause of morbidity and mortality in adulthood (Figure 5). Adults with CHD may present with several different arrhythmias. Accessory pathways are present in ≈20% of the patients with Ebstein anomaly.35

Intra-atrial re-entrant tachycardia is the most common mechanism of arrhythmia in the ACHD population. These arrhythmias cause debilitating symptoms even if the ventricular rate is controlled well. A 1:1 conduction can cause
hypotension, syncope, and even cardiac arrest. Atrial fibrillation is mainly the result of hemodynamic stress in the atrium, and the most common associated lesions are aortic stenosis, mitral valve malformations, and an unrepaired single ventricle. The incidence of these arrhythmias, associated with the severity of the defect, occur often postoperatively, and the incidence generally increases as the patient ages (Figure 4).

Serious ventricular arrhythmias are rare among CHD patients during the first 2 decades of life, but once adulthood is reached, ventricular tachycardia and sudden death become a serious risk associated with ventriculotomy, certain ventricular septal defects, the severity of the defect, tetralogy of Fallot, and severe ventricular dysfunction. Several risk models have been developed.

Sinoatrial node dysfunction is also a common disorder in adults with CHD, caused by isomerism syndromes with absent or dual sinoatrial nodes or caused by direct surgical trauma to its artery during surgical procedures, such as Mustard, Senning, Glenn, and Fontan procedures. Symptoms, low resting frequencies, or pauses over 3 seconds are standard indications for pacing therapy. Similarly, pacemaker therapy is indicated for atrioventricular block in CHD, caused by displacement of the atrioventricular node in congenitally corrected transposition of the great arteries and atrial ventricular septal defect or because of mechanical or hypoxic stress in surgical and interventional procedures.

The burden of arrhythmias and bradycardias is high, for example, in tetralogy of Fallot, as many as one third of patients with repaired tetralogy develop symptomatic atrial tachyarrhythmias by adulthood, 10% develop high-grade ventricular arrhythmias, and 5% Fallot patients require pacemaker implantation for surgically acquired atroventricular block or sinus node dysfunction. After Senning or Mustard repairs for transposition of the great arteries, loss of sinus rhythm occurs in 60% of patients in the 20-year period after surgery. Prevention is attempted with further refinements in surgical strategies, which has resulted in promising reductions of the incidence of arrhythmias. Next to medication and pacemaker therapy, catheter ablation and rarely surgical intervention are treatment opportunities.

**Pulmonary Arterial Hypertension**

Pulmonary arterial hypertension (PAH) is mainly caused by intracardiac left-to-right shunting, leading to pulmonary volume overload. Increased volume and pressure load may cause irreversible endothelial dysfunction and elevated pulmonary vascular resistance, ultimately resulting in a reversal of the left-to-right shunt, leading to central cyanosis, a condition first described by Victor Eisenmenger in 1897. PAH in CHD is stratified into 4 categories according a clinical classification: (1) Eisenmenger syndrome, (2) PAH associated with prevalent systemic-to-pulmonary shunts, (3) PAH with small/coincident defects, and (4) PAH after defect correction. The latter is the most frequently observed patient category. The prevalence of PAH is estimated to be 3.2% in adults born with a systemic-to-pulmonary shunt and 100 per million in the general adult population. PAH prevalence increases with age, from 2.5% under 30 years to 35% in the eldest. The prevalence of Eisenmenger syndrome is estimated to be 4% in leading tertiary centers.

Almost all CHD patients with PAH are symptomatic, half of them in New York Heart Association classification 3 or 4. The possible pharmaceutical interventions have been extended dramatically with currently therapy proven to reduce mortality and morbidity. The oral prostacyclin receptor agonist (Selexipag) is the latest gain in the treatment arsenal. However, survival of Eisenmenger patients still shows only limited improvements over time.

Given the poor outcome and disabling disease course of PAH, much interest has grown to detect the early phase of PAH. Among patients with open and closed shunts, the prevalence of suspected early pulmonary vascular resistance appeared to be 21%, identified by exercise echocardiography using the Master 2-step test. Although clinical studies with Bosentan showed a decrease in dynamic pulmonary vascular resistance, no clinical benefit of early treatment has been demonstrated to date.
Fontan patients do not have pulmonary hypertension but might suffer similarly from relatively increased pulmonary vascular resistance, which turns out dramatically for their clinical performance and prognosis. Several trials with PAH medication has been performed in Fontan patients, with mixed results on improvement on exercise capacity, exercise time, and functional class. With the improvements in care, it is anticipated that the prevalence of PAH in adults with CHD will continue to decrease because many shunts are now closed by surgical or interventional means before pulmonary vascular disease can develop. However, former shunt patients remain at risk of developing PAH, especially above the age of 50 years.

**Endocarditis**

In the general population, the incidence of infectious endocarditis has remained unchanged over the past 4 decades. However, among adults with CHD with its increase in population and the implantation of additional targets for infections, such as shunts, conduits, and prostheses, the incidence has been rising. In a large center in Lyon, France, there were 3.5 cases per year before 1990, increasing to 6 per year after 1990. Currently, the incidence of infectious endocarditis in patients with CHD varies between 1.4 and 11.5 cases per 1000 patient-years. The most frequent complications of infectious endocarditis are increased valvular regurgitation (30%), cardiac failure (23%), and systemic emboli (20%). In contrast, endocarditis in Melody valves seem to lead to obstruction of the artificial valve. The complication rate and early mortality associated with infectious endocarditis in patients with CHD showed a modest decline from 9% to around 7% over the past 2 decades, possibly as a result of improved diagnostics, including echocardiography, computed tomography, and positron emission tomography imaging, earlier and more efficient surgical treatment in 20% of the cases, and improved antibiotic management. Streptococci remain the most common causative organisms followed by staphylococci species and upcoming the propionibacterium acnes. Main focus should be on prevention with attention to education, dental surveillance, and avoidance of skin infections.

**Comorbidity**

The older CHD patient may develop acquired cardiovascular disease, such as hypertension, hyperlipidemia, and diabetes mellitus. This may have an additional impact on the abnormal myocardial substrate, physiology, and anatomy, increasing the risk for ventricular dysfunction, rhythm disturbances, and heart failure. Growing attention for prevention is mandatory as already ≈80% of all adults with CHD has at least 1 cardiovascular risk factor. Hypertension, already highly prevalent in the general population, seems to be even more present in the ACHD patient, especially male, those with a repaired coarctation, and patients with renal disease associated with cyanotic CHD. Obesity, associated with hypertension, insulin resistance, and dyslipidemia, has become a growing problem in the ACHD population, with a prevalence of 54% of patients with a body mass index >25 kg/m² and 20% with a body mass index >30 kg/m². In the Quebec Congenital Heart Disease Database, dyslipidemia has been reported in 27% of the patients >65 years of age. Diabetes mellitus is as common as in the general population, but an abnormal glucose metabolism appeared to be highly prevalent (44%) in a consecutive cohort of 205 adults (mean age 24 years) with complex CHD. Some degree of renal failure was present in almost half of the patients.

It is uncertain whether malignancies are a future threat to adults with CHD because of excessive radiation in the highly susceptible period of childhood, for example, ≈33 mSv has been used in children with tricuspid atresia. However, conflicting results have been published. The Toronto group did not detect excess cancer in 4000 patients, with at least 1 catheterization, while an Israeli study found an excess risk of cancer, with lymphoma and melanoma being most common. Better equipment and shielding methods next to increased use of magnetic resonance imaging and echo-guided decisions will reduce the radiation exposure and subsequent risk on cancer.

Signs of depression (in 9% of the patients) and anxiety (27%) were found to be common in a relatively healthy adolescent population with heart disease. Enhanced awareness and appropriate referral or inclusion of a mental health professional to the CHD care team for treatment and prevention might improve quality of life of adults with CHD. These new challenges of competing illnesses will force current care to adopt new diagnostic and therapeutic strategies in current care.

**Diagnostics**

**Echocardiography**

Fetal echocardiography has brought tremendous progress in the prenatal diagnosis of CHD, allowing improved counseling of the parents, guiding the timing and optimal location of delivery, and appropriate planning and consultation between the cardiologist and neonatologist. It also facilitates accurate diagnosis and management of fetal arrhythmias and serves as the imaging guidance technique for interventions as in utero dilatation of valves, relieving a severe obstruction in an attempt to stimulate growth of a hypoplastic ventricles. Since the introduction of fetal echocardiography, the outcome of newborn patients has further improved.

Transthoracic and transesophageal echocardiography have improved enormously in its imaging quality. New echo techniques have been introduced like tissue Doppler imaging and strain analysis, but all waiting for large-scale validation in CHD patients. Three-dimensional (3D) echocardiography enables calculation of ventricular volumes comparable to cardiovascular magnetic resonance imaging (CMR) measurements. It also is indispensable to guide cardiac interventions like ASD closures, closure of paravalvular leakages, and valve dilatation. A new promising development has been the fusion of echocardiographic and x-ray fluoroscopic imaging in the catheterization laboratory. It seems to be superior in most of the cases, with some reductions in fluoroscopy time and radiation dose.

**Cardiovascular Magnetic Resonance Imaging**

CMR has emerged over the past few decades as an alternative, complementary, and frequently superior imaging modality for the investigation of anatomy and function in the ACHD
patient. It has many advantages over other imaging modalities because it is not limited by poor acoustic windows nor does it require iodinated contrast agents or does it involve exposure to ionizing radiation. Rapid, high-resolution imaging of complex anatomy and accurate quantitative assessment of physiology and function have become possible because of advances in hardware and software, including coil design, faster gradients, new pulse sequences, and faster image reconstruction techniques. Several techniques can be used, such as cine CMR, spin-echo imaging, flow quantification, Gadolinium-enhanced 3D angiography, perfusion imaging, and myocardial viability. With these techniques, a better understanding of anatomy and function can be obtained. A large amount of new data will become available with 3D CMR flow, with information on flow patterns, wall shear stress, and energy loss in several clinical conditions like bicuspid aortic valve, post coarctation patients, and those with a Fontan circulation.

Other Imaging Modalities
Similar for CMR, computed tomography has emerged as a useful tool for assessing (extra) cardiac structures, like aortic dimensions, intracardiac anatomy, coronary artery anatomy, and myocardial function, in the adult with CHD, with reduction in the radiation dose.

Positron emission tomography has been a research tool for many years, allowing in vivo imaging of metabolic, physiological, and pathological processes. It has evolved into a clinically indispensable imaging examination, for example, for prognosis of patients with idiopathic PAH, in assessing novel therapies for PAH, but also for the detection of inflammation in patients suspected of endocarditis. Fusión hybrid coronary computed tomography angiography and positron emission tomography–myocardial perfusion imaging may provide added value for the management of patients with complex coronary artery anomalies, incorporating information on morphology and on quantitative myocardial perfusions.

Upcoming techniques are 3D printing, in which computed tomography or CMR data may be used to reconstruct the heart and vessels. These models can be used to precisely visualize complex anatomy, plan surgical procedures, and teach trainees and patients. Another promising technique is the computer-generated real-time digital holography. Because current 3D images are displaced as a single plane on a 2-dimensional screen, it precludes direct interaction and hampers the perception of depth and spatial relationships. These limitations can be overcome by creating a 3D real-time color dynamic holograms facilitating intervention cardiologist and cardiac surgeon to explore the exact anatomy.

Biomarkers
Biomarkers are becoming increasingly used in patients with CHD as clinicians start to recognize the diagnostic and prognostic significance in CHD patients. BNP (brain natriuretic peptide), a cardiac hormone secreted by cardiac myocytes, respond to ventricular wall stress secondary to volume and pressure overload. Its diuretic, natriuretic, and vasodilatory effects alleviate the detrimental effects of heart failure. BNP values are elevated in most adults with complex CHD; however, conclusions for individual patients still have to be drawn with caution because BNP values differ widely. Troponins are highly specific biomarkers of myocardial damage. They have been traditionally used to identify myocardial infarction; however, these biomarkers are also released in patients with chronic heart failure and pulmonary hypertension, that is, an inverse relationship was found between troponin level and survival in patients with pulmonary hypertension because of CHD. Soluble suppression of tumorgenicity 2 is a promising biomarker of myocardial fibrosis and remodeling in heart failure. It is often expressed in response to myocardial stress and, therefore, may serve as a useful biomarker in patients with both acute and chronic heart failure. Other upcoming biomarkers are galectin, procaldesin, growth differentiation factor 15, adrenomedullin, and cystatin C. Although the exact position of biomarkers still needs to be determined, they will be soon incorporated in daily clinical practice for risk stratification and optimizing therapeutically regimen.

Evolving Concepts
E-health is an important upcoming modality with a high potential of implementation. E-health is a concept covering several processes from telemedicine, teleradiology, teleconsulting, monitoring vital signs, to educational websites, and more. The greatest impact seems to be in early diagnosis of complications. Significant results have also been achieved in the second opinion consultation of pediatric subjects with CHD, in home monitoring, in the management of patients affected by chronic heart failure, and in those with an implanted device. Disappointing results have been found in tailored e-Health intervention to health education and individual counseling among adolescents with CHD.

Over the past years, several new devices have expanded the possibilities of monitoring and detecting subclinical complications. For example, the implantable hemodynamic monitoring system, CardioMeMs, has been developed, and it measures the pulmonary artery pressure daily. With this device, the amount of hospitalizations was reduced in heart failure patients because of acquired heart disease. Mobile chest-adherent devices have been developed, providing continuously wireless recording of accelerometer data from patients in an in-home setting. It can also monitor heart rate, heart rate variability, respiratory rate, and fluid status. Multicenter clinical trials in patients with heart failure because of acquired disease are already initiated. ACHD patients will follow soon. Implantable and external loop recorders can monitor patient for months to detect clinical or subclinical arrhythmias. In these patients, the addition of oral anticoagulation should be considered for primary prevention of stroke. These devices can also be beneficial in patients with neurodevelopmental delay with syncope where accurate history is often limited. As pointed out before, because of major improvements in microelectronics, new diagnostics have been created and existing one further perfected.

Interventions
Medication
In the previous century, medical therapy was mainly based on pathophysiological considerations or parallels with acquired
heart disease. For example, the European Society of Cardiology guideline of 2010 recommends digoxin as the cornerstone of systemic right ventricular failure, although no clinical evidence is available. Over the past decades, a large amount of research has been performed to detect the benefit of pharmaceutical interventions in patients with CHD. Specific populations have been studied more and more, for example, several studies with β-blocking agents and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were performed in patients with systemic right ventricles, although with mixed findings. However, by performing these trials, more knowledge has become available about benefits of specific medication, but it has also led to a better understanding of pathophysiology. For PAH, many different trials have been performed evaluating clinical and hemodynamic parameters, biomarkers, quality of life, and more recently clinical events, including mortality. Bosentan, sildenafil, riocugat, and prostacyclin are all pharmaceutical interventions with benefit in the treatment of PAH, and they changed the prognosis of, for example, Eisenmenger patients dramatically. Other examples of pharmaceutical studies in CHD are rosuvastatin in the progression of aortic stenosis, ramipril on the right ventricular function in Fallot, exercise capacity in Fontan patients with Bosentan, and losartan in Marfan syndrome. Although conducting adequate trials are greatly needed, to come to more evidence-based medicine, increasing costs, lack of funding, and the growing administrative load have a negative impact on this evolution.

**Catheter-Based Procedures**

For a long time, surgery has been the cornerstone in the treatment of patients with CHD. With the development of catheter techniques, percutaneous interventions have replaced some forms of surgery but also extended the therapeutic arsenal (Figure 6). For example, percutaneous closure of atrial septal defect type 2 has become the preferred treatment, except for large or eccentrically positioned defects, for which surgery may still be preferred. Procedural technique and available devices have rapidly advanced since King reported on the first transcutaneous closure of an atrial septal defect type 2 in humans in 1976. A large collection of devices has been developed and tested for its closure rate, overall safety, ease of deployment, retrievability, and ability to close large defects. Erosion of the aorta is one of the main concerns nowadays. Surgical closure of patent ductus arteriosus has been performed for >60 years. Transcatheter closure of a patent ductus arteriosus was introduced in 1967 and has become the preferred treatment for most patent ductus arteriosus after the neonatal period. Transcatheter embolization has become the preferred treatment for aorto-pulmonary collaterals, pulmonary arteriovenous fistulas, venous collaterals, and coronary artery fistulas, replacing surgical intervention in most cases. Percutaneous attempts to close defects have expanded to all types of ventricular septal defects, but these results have been less successful. Balloon valvuloplasty for aortic and pulmonary valve stenosis is feasible if no calcification is present. In the past 10 years, major advances have been made with percutaneous implantation of artificial valves in pulmonary valve position, limiting the number of operations needed over the total lifetime of patients with right ventricle-to-pulmonary artery conduits. Additional developments have been deployed in hybrid procedures combining right ventricular outflow tract replacement with hybrid branch pulmonary artery stenting. Technical changes and awareness initiatives reduced the radiation dose in CHD patients undergoing cardiac catheterization, thereby, limiting the reverse side of catheter-related interventions.

**Devices**

Sudden cardiac death has an important contribution in the reduced survival of patients with CHD. The introduction of cardiac devices with the ability of restoring cardiac rhythm in case of life-threatening arrhythmias has had a major impact on the treatment possibilities of CHD patients. One of the first
analyses on outcome of internal cardiac defibrillators in Fallot patients was performed in 2008. In this multicenter study, clinical risk factors for appropriate shock were determined, and a risk model was constructed subsequently. This model has been adopted widely, with a major impact on the treatment of these patients. Because sudden death is not limited to Fallot patients, as it may occur in all types of CHD, even in those with a mild lesion, there remains a strong need for further prospective studies, as well as vigilant ongoing follow-up of all adults with CHD. Although the cumulative beneficial effects are likely to be greater in ACHD patients than in patients with acquired heart disease, the high rates of inappropriate shocks and complications urge a case-by-case weighing of costs and benefits.

Cardiac resynchronization therapy is an established therapy in patients with acquired heart disease with medically refractory heart failure. Although cardiac resynchronization therapy has been reported to be effective in small series of CHD patients, and in perioperative management, the Guidelines of the European Society of Cardiology in 2013 did not provide specific recommendations. In the end, heart failure has a poor prognosis, despite all efforts with medical therapy, cardiac resynchronization therapy, and implantable cardioverter-defibrillators. The numbers of useable donor hearts available to perform heart transplantation for these patients remain low and inadequate. In the past decade, mechanical circulatory support of the circulation with ventricular assist devices has been evolved rapidly. Ventricular assist devices are devices that assist and support the circulation. They are being inserted into an increasing number of patients with advanced heart failure and are often life-saving. These mechanical circulatory support devices can now be used as bridge to cardiac transplantation, in determining transplant eligibility, as destination therapy, or as bridge to recover. Several pumps have been developed with currently the third generation of devices (Heart ware, Heart mate) for single ventricle support and for biventricular support devices like thoratec paracorporeal assist device and the total artificial heart.

The percentage of patients with CHD who have undergone cardiac transplant is far below 5% of the transplanted population. The initial outcome in CHD patients is worse compared with that in other groups of transplanted patients with a higher risk of graft failure and a 2-fold risk of mortality. However, long-term survival after transplant is best in patients with CHD compared with that in patients with other pretransplant diagnosis. Although assist devices and cardiac transplant for patients with CHD are still used on a limited scale, it is a rapid-evolving medical area and highly relevant for all clinicians seeing patients with CHD.

Surgery
Since the first successful ligation of a PDA in 1938, large-scale intracardiac repair started after the development of cardiopulmonary bypass technology in the 1950s. The possibility of deep hypothermia with circulatory arrest in the 1970s has made cardiac surgery a tremendous success in the reduction of morbidity and mortality of patients born with CHD. More importantly, progress and new developments are still being used, for example, the approach of aortic root surgery has changed dramatically over the past years (Figure 6). Initially total root replacement with a valved conduit was the operation of choice for patients with a dilated aortic root, irrespective of the function of the aortic valve. The operation restores for certain the aortic valve function and eliminates the risk of aortic root dissection but has thromboembolic and bleeding risks in the long run. Since the beginning of this century, valve sparing root replacement has shown excellent short- and long-term results. Valve sparing root replacement offers freedom from anticoagulation and attendant risks of bleeding but a small risk on severe aortic regurgitation necessitating subsequent reoperation with an incidence around 1.3% per year. Recently, a more preventive approach has been launched using a personalized external aortic root support with a mesh sleeve to reduce aneurysm formation in these patients.

The nature of the population of patients referred for surgical therapy has changed over the past years from repairing initial defects to reoperations of complications after initial successful surgery. The expressions cured and total correction appeared to be misconceptions because many late complications may occur often necessitating reoperation. As late referral is common with a deleterious effect on long-term survival, lifelong follow-up is necessary with awareness for residual sequelae of their complex anomalies. Data from the CONCOR registry showed that over the past decade now, 40% of all surgical interventions are reoperations, with a predominance for men. The prognosis of patients who undergo a reoperation, especially their third or fourth, is remarkably worse compared with those without reoperation (Figure 7).

**Pregnancy**
Women with CHD express their desire to give birth to a baby. Based on a limited number of cases, it became soon apparent that women with CHD were at risk for maternal mortality and morbidity. Eisenmenger and heart failure appeared to be the major risk factors. Parallel to guidelines and consensus statements, ongoing clinical research developed models to assess the risk on maternal and neonatal complications. The CARPREG study, a prospective multicenter study of pregnancy outcomes in women with heart disease, reported a 13% complication rate as pulmonary edema, arrhythmias, stroke, and cardiac death. In 20% of patients, there were major neonatal complications. The developed risk score was the first to add clinical assessment on pregnancy outcome. Several other risk scores became subsequently available. Mechanical valves, impaired function of the ventricle, and severe obstruction were increasingly identified as additional determinants of complications. A continuing clinical hurdle remains the management of anticoagulation in woman with mechanical valves. To date, there is no ideal anticoagulation strategy; all regimens have their inherent risks and benefits for mother and fetus.

As most women with CHD will consider to become pregnant, nowadays these patients are recommended to be seen by clinicians in these centers. Dedicated clinicians are better prepared (1) in preconception counseling, including risk assessment, (2) to give appropriate contraceptive advice, and (3) to take care of close monitoring during and after pregnancy, with close interaction with obstetrician to minimize risks for
mother and child. The global ROPAC registry, a multicenter collaboration on pregnancy outcomes in women with heart disease, will provide more data in the future.122

Sports
All children have a natural need to move, play, and perform activities, and physical activity is necessary for their development. But also for adults, it is recommended to perform exercise 3 to 5 times a week.123 However, patients with CHD used to be over restricted by physicians, parents, and educators because of misperceptions about risks and benefits.124 Nowadays, still many patients with CHD have a reduced exercise capacity and a reduced level of physical activity.125 As exercise capacity seems to be an important predictor of health outcome and survival, much effort has been put in determining the benefits of exercise programs in these patients. A recent randomized trial including patients with a systemic right ventricle showed improvement of exercise capacity without adverse events.126 Also in patients with a high risk on sudden death, combined aerobic/resistance training appeared to be safe, even resulting in a reduction in ventricular arrhythmias.127 Apart from the specific benefits on CHD, regular physical activity and exercise lead to the adoption of a healthy lifestyle, which at the end may be beneficial to prevent acquired heart diseases later in life. It may also improve motoric, emotional, social, and intellectual performance. Guidelines have been developed to support the clinicians in their individual clinical judgment to advise on exercise and sports participation.124 Future research will elucidate the evidence of long-term risks and benefits of sports participation in adults with CHD.

Clinical Research
Research on ACHD has changed dramatically: from case series and retrospective studies to prospective cohorts and randomized controlled trials. Nevertheless, with the increasing administrative load and increasing costs, the amount of trials will still rise. Hopefully, this increase in scientific quality will further support the guidelines because they are still mainly based on expert consensus.

Important progress has been made in the investigation of the relationship between genetic factors, clinical features, and outcomes in CHD. The Pediatric Cardiac Genomics Consortium is a consortium with this topic as focus.128,129 It comprises 6 main and 4 satellite sites at which subjects are recruited, and medical data and biospecimens are collected. Several studies have been initiated, eg, whole-exome sequencing in trios to identify homozygosity for rare variants to predict which are to be damaging and alter genes relevant for cardiovascular development. With the analysis of copy number variants, research is initiated to search for inherited or de novo copy number variants that contribute to the pathogenesis of CHD and to investigate the relation of point mutations and indels in candidate genes with CHD. In the past decade, much effort has been put to understand how genetics and hemodynamic loading contribute to heart failure in CHD. This research will provide more insights into the fundamental
principles of cardiac physiology and its transition into heart failure, for example, the impact of mutations in key transcription factors in cardiac malformations and an altered response in postnatal period to stress and growth. Also, recent mice studies showed that different Noonan syndrome genes have intrinsically distinct pathological effects, suggesting a mutation-specific approach to the treatment of RASopathies (syndromes caused by germline mutations).130,131

Networks have been founded on a national level like the Alliance for Adult Research in Congenital Cardiology in the United States and the Canadian Adult Congenital Heart Network in Canada. International networks like the International Adult Congenital Heart Disease Nursing and the International Society on Adult Congenital Heart Disease facilitates worldwide collaborative ACHD research and education, similar to the Euro Grown-Up Congenital Heart Disease Working Group for Europe. Several international initiatives have been undertaken to improve efficacy of studies, for example, the NOTE Registry, a global study assessing the efficacy and safety of non-vitamin K oral antagonists in preventing thromboembolic complications in adults with CHD and atrial arrhythmias, and the ROPAC study, describing the outcome of pregnancy in cardiac patients, including ACHD.

During the past 20 years, several clinical guidelines106 and recommendations on staff and institutional needs to run an ACHD program have been published. This approach had a positive impact on the healthcare organization and the quality of the delivered care. One of the first clinical guidelines was presented at the 1996 CCS conference and published in 1998, followed by several other proposals. Because of these initiatives, specialized medical care was increasingly delivered to adult patient with CHD, resulting in a dramatic increase of referral to the specialized ACHD centers (rate ratio of 7.4%) and a significant reduction in mortality of −5.5%.132 This was specifically seen in patients with severe CHD.

The availability of information on the Internet has made a dramatic change for healthcare employees. In the past, the library was the place to be to gain information on disease, research publications, and other information. Nowadays, online data are widely available, including books, research papers, but also clinical presentations from congresses, webinars, upcoming trials (clinicaltrials.org), and books. This facilitated a rapid access to information easily to tailor on individual patients. Websites like http://achdlearningcenter.org are excellent developments in providing up-to-date papers, network connections, and educational modules. Also patients retrieve information from all over the Internet forums and magazines, being often well informed about diagnostics and therapies prepared for shared decision making.

The improvement of computers had great impact on medical statistics. Many researchers have developed skills to perform difficult data analysis like meta-analysis, mixed models, left censoring, and metadata analysis, which increased knowledge on for example, epidemiology, associations, and interventions.

**Organization**

In the past, pediatric cardiologists followed their patients throughout their entire lives. The increased life expectancy, the changing clinical presentation of adult patients, and the comorbidity appearing in elder patients forced a change in the organization of health care. ACHD patients were no longer treated in children’s hospitals, and ACHD specialized cardiologist became a recognized subspecialty within cardiology. Specialized ACHD services began to develop. In 1979, the first clinic in ACHD was established in Toronto, followed by Europe in 1964; within 2010, in the European Union, over 70 specialized ACHD centers were established.133 Although specialized centers are strongly associated with a reduction in mortality, still only 8% of the patients who need it receive it.134

With the upcoming ACHD centers, it became apparent that transition from pediatric cardiology to adult was an important issue to ensure lifelong surveillance to reduce the elevated risk on premature death, hospital admissions, heart failure, and arrhythmias. Transition, a process that addresses the medical, psychological, and educational needs of adolescents, has to be initiated at the age of 12 years. Moreover, the period of transition from the pediatric cardiology to ACHD care is a period with a considerable risk for losing contact with the care givers.135 In patients with mild disease, a gap in care has been reported in 59% of the patients, being lower for patients with moderate (42%) and severe disease (26%).136 Patients with none or a low number of heart surgeries, health insurance issues, and non-white ethnicity appeared to have the highest risk of falling out of the system.137 Efforts to retrieve these patients again under medical care have been successful.138 Whether the transition can be improved when specialized nurses are in the lead is uncertain but will probably be answered with the chapter two trial.139 Together with the founding of ACHD specialized centers, also training for pediatric and adult cardiologist has been formalized. Specific requirements are outlined in terms of training duration, numbers of procedures, as well as achieved competencies.

**Conclusions**

Over the past 50 years, the landscape of adults with CHD has changed dramatically. The population has expanded because of the enormous improvements in diagnostics, percutaneous interventions, surgery, and care. Surgical mortality rates are decreasing, and life expectancy will further increase with the future ahead of us. The flip side of these triumphs is the increase of late complications necessitating reoperations, percutaneous interventions, and implantation of devices to reduce late morbidity and mortality. The improvements in clinical research, including trials, intervention studies, and large registries, changed our care to be more supported with evidence. Organization of care aims to deliver care more appropriately to the patient who really needs it. It introduced sports participation to improve quality of life and emphasized the need for proper education. The landscape of ACHD is an ongoing evolving process demanding worldwide efforts of all caregivers to come to optimal care for this large, still expanding, chronic ill population.

**Disclosures**

None.
References


Pizzi MN, Roque A, Ponzanelli JT, Bartz AJ, Timoner M, Clerc OF, Mikulicz F, Vontobel J, Stehli F, Jous A, Paizhenkotill AP, Gaemperli O, Kaufmann PA, Buechel RR. Fused cardiac hybrid imaging with coronary computed tomography...


Changing Landscape of Congenital Heart Disease
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