Editorial

Prognosis is better, still not good, and variable, for adults with congenital heart disease

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Over the last decades we have witnessed a significant improvement at the prognosis in children with congenital heart disease with more than 95% today expected to reach adulthood (1). Despite this change of survival for patients with congenital heart disease, it has been recently described a relative higher risk of morbidity such as stroke and heart failure, and late mortality compared to persons without congenital heart disease in a similar age and sex (1,2). While in general mortality may be higher for adults with congenital heart disease (ACHD), these patients represent a wide spectrum of diseases from uncomplicated, self-healing conditions to extremely complex conditions such as the hypoplastic left heart syndrome (HLHS) which carries a very high mortality also in the early years of life, despite recent advances in surgical treatment (3). However, patients with less complex conditions such as ventricular or atrial septal defects have been reported to exhibit a higher mortality as compared to healthy age-matched controls in the long term (4). While little doubt exists regarding the higher mortality for ACHD, less is known on the impact of previous repair and modifiable factors on the late mortality. Oliver and colleagues analyzed a large single center population of 3,311 ACHD, followed for an average of 10.5 years and seen at the ACHD-Unit at the "La Paz University Hospital" in Madrid, Spain, and reported their results in a recent paper in *European Heart Journal* (5). The investigators used data from the local hospital database that was initiated in 1989 and prospectively register all ACHD patients until the end of 2013; the records of 3,764 individuals making it one of the larger single-center registries available. For the present analysis they excluded 314 (8.3%) of all individuals with diagnosis that are frequently encountered in most ACHD-units, while not being strictly morphologic, anatomic congenital defects such as patent foramen ovale, mitral valve prolapse and coronary artery anomalies. In addition, another 139 patients lacked complete demographic data and were also excluded from further analysis, leaving a total of 3,311 patients (88%) for further analysis. Among these patients, 336 (10%) died after a median follow-up of approximately 10 years.

Almost half the patients in this cohort had a simple CHD, according to the Bethesda classification of ACHD (6) with a mortality of 9.4%, another 39% were classified as patients with moderate defects and had a death rate of 7.5% and the remaining 12% of the ACHD patients were classified as severe defects with a death rate of 21% over 8.4 years of follow-up.

The authors analyzed outcome in relation to repair: childhood, adult, no indication for repair or non-repairable. A total of 1,382 patients were repaired in childhood (42%) while an additional 22% underwent repair later in life and these two groups had similar outcome. The lowest standardized mortality rate (SMR), i.e., mortality compared to the Spanish reference population and adjusted for age, sex and age at diagnosis was observed among the 31% of patients where there was no indication for repair.

Overall, the mortality rate in relation to the reference population was more than twice as high (2.6), most notably among patients with the most severe conditions that the SMR was 21.7, in relation to the moderate cases with SMR of 3.1 and 1.7 (95% CI, 1.4–2.0) for patients with the least complex conditions. This is very much in line with previous studies (1,7) and clearly demonstrates that although mortality has dramatically declined for children born with congenital heart disease, the relative risk of dying is still very substantial, also in milder cases in general.

The study also provides data on SMR in relation to diagnostic categories in more detail. Some findings are intuitive and confirms previous studies such as the low SMR (ns compared to controls) for patients with VSD and pulmonary stenosis. However, more surprising is the finding of the doubled SMR for patients with patent ductus arteriosus, a condition generally believed to be very mild and easily treatable and in many cases possible to cure by an easy catheter intervention. The SMR of 2.2 in the study by Oliver *et al.* possibly reflects an older era where some patients may have gone undetected for significant time (until LV failure and/or pulmonary hypertension affects the patient) or where a surgical approach was not always without complications, albeit on the low end of the spectrum. To be expected are the findings of a very high SMR among patients with single-ventricle physiology or pulmonary vascular disease.

But the recent report from Oliver and colleagues also sheds some light on the risk factors for excess mortality and in this respect very much adds to the present knowledge and present a comprehensive list of the most important factors among their patients. Genetic syndromes, subpulmonary ventricular dysfunction, clinical cyanosis and pulmonary outflow tract obstruction was associated with a HR of about or above 2.0 as well as pulmonary hypertension and infective endocarditis and single ventricle physiology. No surprise so far, but the authors report that moderate or more pulmonary, tricuspid or aortic regurgitation was surprisingly not associated with a significantly increase risk, nor was the presence of a systemic right ventricle associated with a significantly increased risk. On the other hand, systemic ventricular dysfunction, which is much more likely to occur if the systemic ventricle is indeed of right ventricular morphology, gave a HR of 1.7. Atrial flutter or atrial fibrillation was not related to an increased risk, which is contradictory to other previous reports from large population studies (8).

The authors also calculated the effect these risk factors had on the SMR and found that clinical cyanosis and single ventricle physiology were strong risk factors, with a SMR of close to 30. Perhaps more surprisingly, they also found that endocarditis and atrial flutter/fibrillation as well as ischemic heart disease, all of which may be either prevented, treated or at least minimized, were all associated with a significant increase in SMR of between 3 to 10 times. This is somewhat in line with the findings reported by Diller *et al.* (9) who described an increased mortality among patients who were in active follow-up at their institution in compared to a general population sample. However, Diller *et al.* also found that heart failure and pneumonia were the prime causes of death for their population, while sudden death was less common. This was, somewhat surprisingly, most pronounced among patients with conditions notorious for their propensity for sudden death, i.e., tetralogy of Fallot where sudden death was the sixth most common cause of death, possibly reflecting a selection bias.

The perhaps most important, and encouraging finding in the study by Oliver *et al.*, is the low risk of the 66% of their patients that had no risk factor as describe above: those patients had a SMR of 1.06 (95% CI, 0.8–1.4) (5). For the majority of patients seen at an ACHD-unit, the risk of death is, in comparison with age- and sex matched controls without congenital heart disease, very similar although the non-significant difference observed here may be a bit optimistic. However, the focus of attention could and should be on those patients that have a substantial increase in risk and in particular to those where the risk is present due to something that may be treatable and/or preventable. Meticulous treatment of ventricular dysfunction and identification, treatment, and possibly prevention, of endocarditis will minimize the impact of the congenital malformation. The risk of atrial fibrillation, potentially leading to stroke, the risk of which is markedly increased in ACHD-patients (2), can be minimized by early and vigilant detection and treatment of atrial arrhythmias including adequate anticoagulation.

There are, as in any retrospective, registry based study a number of limitations to the present study. While there was an acceptable level of lost to follow-up and data were entered in a prospective manner in the registry, there are several factors of which we know very little. Conventional risk factors, i.e., physical inactivity, smoking, hyperlipidemia, hypertension and diabetes are not known or reported. The presence of a congenital heart condition offers no protection against conventional cardiovascular disease and we have reason to believe that ACHD patients

have an increased risk of developing both type 1 and type 2 diabetes and this may also be associated with an added risk, even more among ACHD patients (10).

Sometimes ACHD patients are called "young people with old hearts" but it is in most more accurate to say "young people with repaired, young hearts", hearts that need meticulous care but also need protection from acquired risk factors such as hyperlipidemia, hypertension or hyperglycemia. For a small proportion of ACHD patients, we need to focus our efforts to provide the optimum care, being very much aware of the, relatively, much higher risk of death that these patients are subject to.

The paper by Oliver *et al*. provides us with a comprehensive examination of the risk of death for patients with ACHD, from a large prospective registry with good follow-up and good quality of data.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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