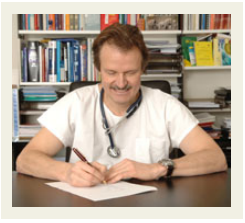
European Heart Journal (2016) **37**, 1407–1409
doi:10.1093/eurheartj/ehw161

Frontiers in congenital heart disease: pulmonary hypertension, heart failure, and arrhythmias



Thomas F. Lüscher, MD, FESC

Editor-in-Chief, Zurich Heart House, Careum Campus, Moussonstrasse 4, 8091 Zurich, Switzerland

Although rare and affecting ~0.8% of all births worldwide, patients with congenital heart disease continue to increase in number. This is mainly due to the fact that children with congenital heart disease are able to reach adulthood today thanks to modern surgical and medical management.[1,2] Residual lesions and the sequelae of previous interventions predispose to higher morbidity and mortality requiring specialized care.[3] Also, for many patients, their later life course is often complicated by endocarditis,[4] pulmonary hypertension,[5,6] arrhythmias,[7] and heart failure,[8] even requiring transplantation in some cases.[9] Due to a lack of large clinical studies on outcome in this patient population, guidelines for heart failure treatment are lacking. Indeed, the management and treatment of patients are therefore not standardized, leading to confusion for patients, treating physicians, nurse practitioners, physiotherapists, and others involved in the management of congenital heart disease. Furthermore, for some patients, drugs for the management of heart failure may even be harmful, especially if the underlying pathophysiology and haemodynamics are not understood. These issues are addressed in a *Current Opinion* '**Treatment of heart failure in adult congenital heart disease. A Position Paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology**' by Werner Budts from the University Hospitals Leuven in Belgium.[10]

A clinical review entitled '**Mobile technology and the digitization of healthcare**' by Partho P. Sengupta from the Mount Sinai Hospital in New York notes that the convergence of science and technology in our dynamic digital era has resulted in the development of innovative digital health devices that allow easy and accurate characterization in health and disease.[11] Indeed, technological advancements and the miniaturization of diagnostic instruments to modern smartphone-connected and mobile health devices such as the iECG, handheld ultrasound, and lab-on-a-chip technologies promise to decrease healthcare costs and to improve outcomes. This 'hype' for mHealth has recently intersected with the 'real world' and is providing important insights into how patients and practitioners are utilizing digital health technologies. It is also raising important questions regarding the evidence supporting widespread device use. In this state-of-the-art review, the authors assess the current literature of mHealth and aim to provide a framework for advances in mobile health by understanding the various device, patient, and clinical factors as they relate to digital health from device designs and patient engagement, to clinical workflow and device regulation. In addition, they outline new strategies for generation and analysis of mHealth at the individual and population-based levels.

Although many patients with congenital heart disease do well after corrective or palliative surgery and/or interventions, arrhythmias and sudden cardiac death are a major cause of mortality in this population.[12] However, indications for implantable cardioverter defibrillators or ICDs are still not well established.[13] In their meta-analysis entitled '**Implantable cardioverter-defibrillators in adults with congenital heart disease: a systematic review and meta-analysis**', Jim T. Vehmeijer and colleagues from the Academic Medical Center of the University of Amsterdam, The Netherlands systematically reviewed the literature on this issue.[14] Overall 2162 patients with a follow-up of 3.6 years from 24 studies, half of them with tetralogy of Fallot, were included. ICDs were implanted for primary prevention in 53%. Of those, 24% of patients received one or more appropriate ICD interventions such as antitachycardia pacing or shocks. All-cause mortality was 10%. Of note, inappropriate shocks occurred in 1 out of 4 patients, as did lead-related

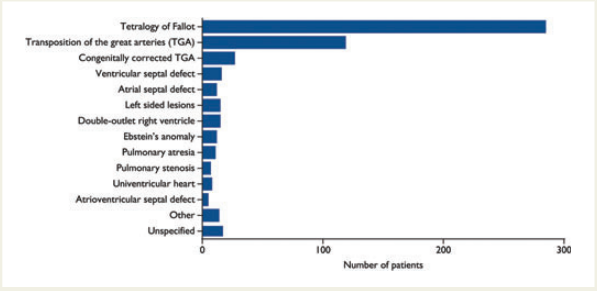


Figure 2 Distribution of congenital heart diseases across 20 studies ($n = 563$).

complications. The authors conclude that in adult congenital heart disease, remarkably high rates of appropriate ICD therapy, in both primary and secondary prevention, are notable. Because of the young age and lower death rates, the cumulative beneficial effects are likely to be greater in this population compared with those with acquired heart disease. However, considering the high rates of inappropriate shocks and complications, the costs and benefits of ICD implantation have to be considered carefully in each patient.

In patients with right-to-left shunt in particular, Eisenmenger syndrome is a major complication.[5] In a second paper, '**Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for Congenital Heart Defects**', Gerhard-Paul Diller from the University Hospital Münster in Germany assessed the contemporary outcome of such patients.[15] Overall, 153 patients with Eisenmenger syndrome with a median age of 34 years were identified from the German National Register for Congenital Heart Defects. Half of these were treated with at least one disease-targeting therapy,[16] mainly bosentan and to a lesser degree sildenafil, while about a fifth were on dual therapy. In addition, a quarter of the patients received digoxin and some inhibitors of the renin–angiogtensin system or beta-blockers. Only 18% were anticoagulated and 24% were on aspirin. The survival rate at 1, 5, and 10 years was only 92, 75, and 57%, respectively. In treatment-naïve Eisenmenger patients, the survival rate was even worse, with 86, 60, and 34% at 1, 5, and 10 years, respectively. Use of disease-targeting therapies was independently associated with a better survival, with a hazard ratio of 0.42. This study reminds us of the alarmingly poor survival of Eisenmenger patients in spite of the availability of modern drugs even in a country with a well accessible healthcare system. Early use of disease-targeting therapies therefore appears mandatory in these patients.

Congenital heart disease not only includes patients with abnormalities of the valves, cardiac chambers, or great vessels, but also those with genetic defects of the conduction system.[17] In particular, the long QT syndrome is associated with a high risk of sudden death.[18] In some patients, the long QT syndrome is acquired due to drugs,[19–21] hypokalaemia, or bradycardia, and also may elicit torsades-de-pointes, ventricular tachycardia, or fibrillation. In the third research paper, '**The genetics underlying acquired long QT syndrome: impact for genetic screening**', Minoru Horie *et al.* from the Shiga University of Medical Sciences in Ohtsu, Japan assessed the prevalence of mutations in major long QT genes in patients with acquired long QT syndrome.[22] They screened for five major long QT genes among 188 individuals. Based on their baseline QTc interval without any trigger, subjects were categorized into true acquired long QT syndrome with QTc within normal limits (i.e. 453 $\pm$ 39 ms) or unmasked congenital long QT syndrome (with QTc of 478 $\pm$ 46 ms). Subjects were compared for QTc and genetics with 2379 members of genotyped families with congenital long QT syndrome. Cardiac symptoms were notable in the vast majority of subjects. In 28% of subjects with acquired long QT syndrome, 47 disease-causing mutations were identified. Compared with those with the congenital form, KCNQ1 mutations were much less frequent than KCNH2, i.e. 20% vs. 64%. A clinical score based on baseline QTc, age, and symptoms allowed identification of patients more likely to carry mutations. Thus, about a third of patients with acquired long QT syndrome carry cLQTS mutations, mainly involving KCNH2. The probability of being a carrier can be predicted by simple clinical parameters, thus allowing for cost-effective genetic testing. The paper is accompanied by an **Editorial** by Arthur Wilde from Experimental and Molecular Cardiology in Amsterdam, The Netherlands.[23]

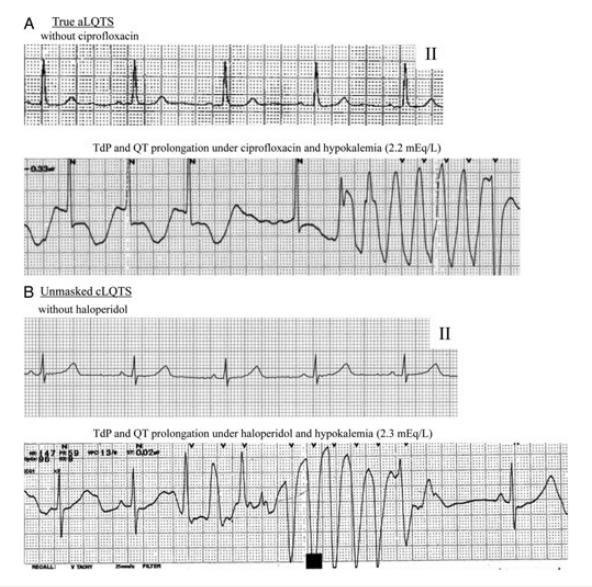


Figure 2 Electrocardiograms of true acquired long QT syndrome and unmasked congenital long QT syndrome. (*A*) A representative case with true long QT syndrome. This 73-year-old female was admitted for the treatment of bacterial pneumonia. Her basal QTc was normal (396 ms, upper panel). Torsades de Pointes and severe QT prolongation appeared 3 days after receiving ciprofloxacin (lower panel) and led to ventricular fibrillation. After cardioversion, the ECG showed marked QT prolongation (613 ms) and atrial fibrillation with hypokalaemia (2.2 mEq/L). (*B*) A representative case with unmasked congenital long QT syndrome. This 52-year-old alcoholic male was treated with haloperidol i.v. (6 mg) for withdrawal symptoms. Though his control QTc interval was prolonged but not remarkably (466 ms), a monitoring ECG showed Torsades de Pointes and marked QTc prolongation (624 ms) after haloperidol accompanied by hypokalaemia (2.3 mEq/L). Genetic analysis revealed a *KCNH2* mutation (R948S) located in the C-terminus.

Ventricular fibrillation, the main cause of sudden cardiac death, occurs most frequently in the acute phase of myocardial infarction: a certain fraction of such arrhythmias, however, develops in an apparently healthy heart, referred to as idiopathic ventricular fibrillation. The contribution of perturbation in the fast conduction system in the ventricle, the His–Purkinje system, to this condition has been proposed, but the underlying mechanism remains unknown. Irx3/IRX3 encodes a transcription factor specifically expressed in the His–Purkinje system in the heart. Genetic deletion of Irx3 provides a mouse model of ventricular fast conduction disturbance without anatomical or contraction abnormalities. In the final paper entitled '**Genetic defects in a His–Purkinje system transcription factor, IRX3, cause lethal cardiac arrhythmias**', Tetsushi Furukawa from Tokyo Medical and Dental University in Japan examined the link

between a perturbed His–Purkinje system and idiopathic ventricular fibrillation in Irx3-null mice, and searched for IRX3 genetic defects in in humans.[24] Telemetry ECG recordings showed that Irx3-deleted mice frequently developed ventricular tachyarrhythmias mostly at night. These arrhythmias were enhanced by exercise and sympathetic nerve stimulation. In the human, the sequence analysis of IRX3 exons in 130 probands of idiopathic ventricular fibrillation without SCN5A mutations revealed two novel IRX3 mutations, 1262G>C (R421P) and 1453C>A (P485 T), which were associated with ventricular fibrillation upon physical activity. In HL-1 cells and neonatal mouse ventricular myocytes, IRX3 transfection up-regulated SCN5A and connexin-40 mRNA, which was attenuated by IRX3 mutations. Thus, IRX3 genetic defects and the resultant functional perturbation in the His–Purkinje system are novel genetic risk factors of idiopathic ventricular fibrillation, and might improve risk stratification and prevention of sudden death in otherwise healthy hearts. The paper is accompanied by an **Editorial** by Geoffrey Pitt from Duke University in Durham, North Carolina.[25]

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

References

1. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, Dimopoulos K, Swan L, Gatzoulis MA, Diller GP. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. *Eur Heart J* 2014;**35**:725–732.
2. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. *Eur Heart J* 2014;**35**:716–724.
3. Baumgartner H, Budts W, Chessa M, Deanfield J, Eicken A, Holm J, Iserin L, Meijboom F, Stein J, Szatmari A, Trindade PT, Walker F; Working Group on Grown-up Congenital Heart Disease of the European Society of Cardiology. Recommendations for organization of care for adults with congenital heart disease and for training in the subspecialty of 'Grown-up Congenital Heart Disease' in Europe: a position paper of the Working Group on Grown-up Congenital Heart Disease of the European Society of Cardiology. *Eur Heart J* 2014;**35**:686–690.
4. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL; Document Reviewers, Erol Ç, Nihoyannopoulos P, Aboyans V, Agewall S, Athanassopoulos G, Aytekin S, Benzer W, Bueno H, Broekhuizen L, Carerj S, Cosyns B, De Backer J, De Bonis M, Dimopoulos K, Donal E, Drexel H, Flachskampf FA, Hall R, Halvorsen S, Hoen B, Kirchhof P, Lainscak M, Leite-Moreira AF, Lip GY, Mestres CA, Piepoli MF, Punjabi PP, Rapezzi C, Rosenhek R, Siebens K, Tamargo J, Walker DM. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;**36**:3075–2128.
5. Dimopoulos K, Wort SJ, Gatzoulis MA. Pulmonary hypertension related to congenital heart disease: a call for action. *Eur Heart J* 2014;**35**:691–700.
6. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barberà J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol Ç, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Völler H, Luis Zamorano J. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;**37**:67–119.
7. Winkel BG, Risgaard B, Sadjadieh G, Bundgaard H, Haunso S, Tfelt-Hansen J. Sudden cardiac death in children (1–18 years): symptoms and causes of death in a nationwide setting. *Eur Heart J* 2014;**35**:868–875.
8. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E; Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;**31**:2915–2957.
9. Meijboom F, de Jonge N. Heart transplantations in adults with congenital heart disease: new frontiers. *Eur Heart J* 2016;**37**:790–792.
10. Budts W, Roos-Hesselink J, Radle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, Crespo-Leiro MG, Walker F, Frogoudaki AA. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* 2016;**37**:1419–1427.
11. Bhavnani SP, Narula J, Sengupta PP. Mobile technology and the digitization of healthcare. *Eur Heart J* 2016;**37**:1428–1438.
12. Semsarian C, Ingles J, Wilde AA. Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives. *Eur Heart J* 2015;**36**:1290–1296.
13. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; Authors/Task Force Members; Document Reviewers. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–2867.
14. Vehmeijer JT, Brouwer TF, Limpens J, Knops RE, Bouma BJ, Mulder BJ, de Groot JR. Implantable cardioverter-defibrillators in adults with congenital heart disease: a systematic review and meta-analysis. *Eur Heart J* 2016;**37**:1439–1448.
15. Diller GP, Korten MA, Bauer UM, Miera O, Tutarel O, Kaemmerer H, Berger F, Baumgartner H, and German Competence Network for Congenital Heart Defects Investigators. Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects. *Eur Heart J* 2016;**37**:1449–1455.
16. Romano S, Chung J, Farzaneh-Far A. Reversal of right-ventricular dysfunction in pulmonary arterial hypertension following sildenafil therapy. *Eur Heart J* 2015;**36**:2018.
17. Brugada P, Brugada J, Roy D. Brugada syndrome 1992–2012: 20 years of scientific excitement, and more. *Eur Heart J* 2013;**34**:3610–3615.
18. Nielsen JB, Graff C, Rasmussen PV, Pietersen A, Lind B, Olesen MS, Struijk JJ, Haunsø S, Svendsen JH, Køber L, Gerds TA, Holst AG. Risk prediction of cardiovascular death based on the QTc interval: evaluating age and gender differences in a large primary care population. *Eur Heart J* 2014;**35**:1335–1344.
19. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur Heart J* 2013;**34**:3109–3116.
20. Fanoe S, Kristensen D, Fink-Jensen A, Jensen HK, Toft E, Nielsen J, Videbech P, Pehrson S, Bundgaard H. Risk of arrhythmia induced by psychotropic medications: a proposal for clinical management. *Eur Heart J* 2014;**35**:1306–1315.
21. Bardai A, Amin AS, Blom MT, Bezzina CR, Berdowski J, Langendijk PN, Beekman L, Klemens CA, Souverein PC, Koster RW, de Boer A, Tan HL. Sudden cardiac arrest associated with use of a non-cardiac drug that reduces cardiac excitability: evidence from bench, bedside, and community. *Eur Heart J* 2013;**34**:1506–1516.
22. Itoh H, Crotti L, Aiba T, Spazzolini C, Denjoy I, Fressart V, Hayashi K, Nakajima T, Ohno S, Makiyama T, Wu J, Hasegawa K, Mastantuono E, Dagradi F, Pedrazzini M, Yamagishi M, Berthet M, Murakami Y, Shimizu W, Guicheney P, Schwartz PJ, Horie M. The genetics underlying acquired long QT syndrome: impact for genetic screening. *Eur Heart J* 2016;**37**:1456–1464.
23. Amin AS, Wilde AAM. Genetic screening in acquired long QT syndrome? CAUTION: proceed carefully. *Eur Heart J* 2016;**37**:1465–1468.
24. Koizumi A, Sasano T, Kimura W, Miyamoto Y, Aiba T, Ishikawa T, Nogami A, Fukamizu S, Sakurada H, Takahashi Y, Nakamura H, Ishikura T, Koseki H, Arimura T, Kimura A, Hirao K, Isobe M, Shimizu W, Miura N, Furukawa T. Genetic defects in a His–Purkinje system transcription factor, *IRX3*, cause lethal cardiac arrhythmias. *Eur Heart J* 2016;**37**:1469–1475.
25. Matsui M, Pitt GS. Genetic variants and disease: correlate or cause? *Eur Heart J* 2016;**37**:1476–1478.