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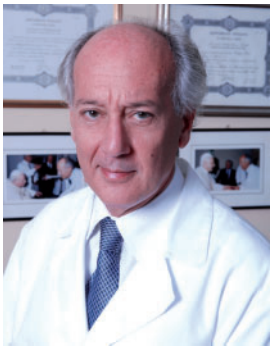
Hot topics in congenital heart disease and new insight into ventricular non-compaction



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This Focus Issue on congenital heart disease contains the Special Article '**Transition to adulthood and transfer to adult care of adolescents with congenital heart disease: a global consensus statement**'.[1] Most children with congenital heart disease (CHD) in high-income countries survive into adulthood. Further, paediatric cardiac services have expanded in middle-income countries. Both evolutions have resulted in an increasing number of CHD survivors.[2–5] In adolescence, patients transition from being a dependent child to an independent adult. They are also advised to transfer from paediatrics to adult care. There is no universal consensus regarding how transitional care should be provided and how transfer should be organized. This consensus document describes issues and practices of transition and transfer of adolescents with CHD, accounting for different possibilities in high-, middle-, and low-income countries. Transitional care ought to be provided to all adolescents with CHD, taking into consideration the available resources. When reaching adulthood, patients ought to be transferred to adult care facilities/providers capable of managing their needs, and systems must be in place to make sure that continuity of high-quality care is ensured after leaving paediatric cardiology.

In a State of the Art Review article entitled '**Management of acute cardiovascular complications in pregnancy**', Gabriele Egidy Assenza from the IRCCS Azienda Ospedaliero-Universitaria di Bologna in Italy and colleagues note that the growing population of women of reproductive age with heart disease has been associated with an increasing number of high-risk pregnancies.[6] Pregnant women with heart disease are a very heterogeneous population, with different risks for maternal cardiovascular, obstetric, and foetal complications.[7–11] Adverse cardiovascular events during pregnancy pose significant clinical challenges, with uncertainties regarding diagnostic and therapeutic approaches potentially compromising maternal and foetal health. This review provides a summary of recommendations on the management of acute cardiovascular complications during pregnancy, based on available literature and expert opinion. The authors cover the diagnosis, risk stratification, and therapy, and the review is organized according to the clinical presentation and the type of complication, providing a reference for the practising cardiologist, obstetrician, and acute medicine specialist, while highlighting areas of need and potential future research. Topics covered include heart failure (HF), arrhythmias, coronary artery disease, aortic and thrombo-embolic events, and the management of mechanical heart valves during pregnancy (*Figure 1*) .

In a Clinical Research article entitled '**Lack of specialist care is associated with increased morbidity and mortality in adult congenital heart disease: a population-based study**', Gerhard-Paul Diller from the University Hospital Münster in Germany, and colleagues aimed to provide population-based data on the healthcare provision for adults with congenital heart disease (ACHD) and the impact of cardiology care on morbidity and mortality in this vulnerable population.[12] Based on administrative data from one of the largest German Health Insurance Companies, all insured ACHD patients (<70 years of age) were included. Patients were stratified into those followed exclusively by primary care physicians (PCPs) and those with additional cardiology follow-up between 2014 and 2016. Associations between level of care and outcome were assessed by multivariable/propensity score Cox analyses. Overall, 24 139 patients (median age 43 years, 54.8% female) were included. Of these, only 50% had cardiology follow-up during the 3-year period, with 49% of patients only being cared for by PCPs and 1% having no contact with either. After comprehensive multivariable and propensity score adjustment, ACHD patients under cardiology follow-up had a significantly lower risk of death [hazard ratio (HR) 0.81; $P = 0.03$] or major events (HR 0.85; $P < 0.001$) compared with those only followed by PCPs. At 3-year follow-up, the absolute risk difference for mortality was 0.9% higher in ACHD patients with

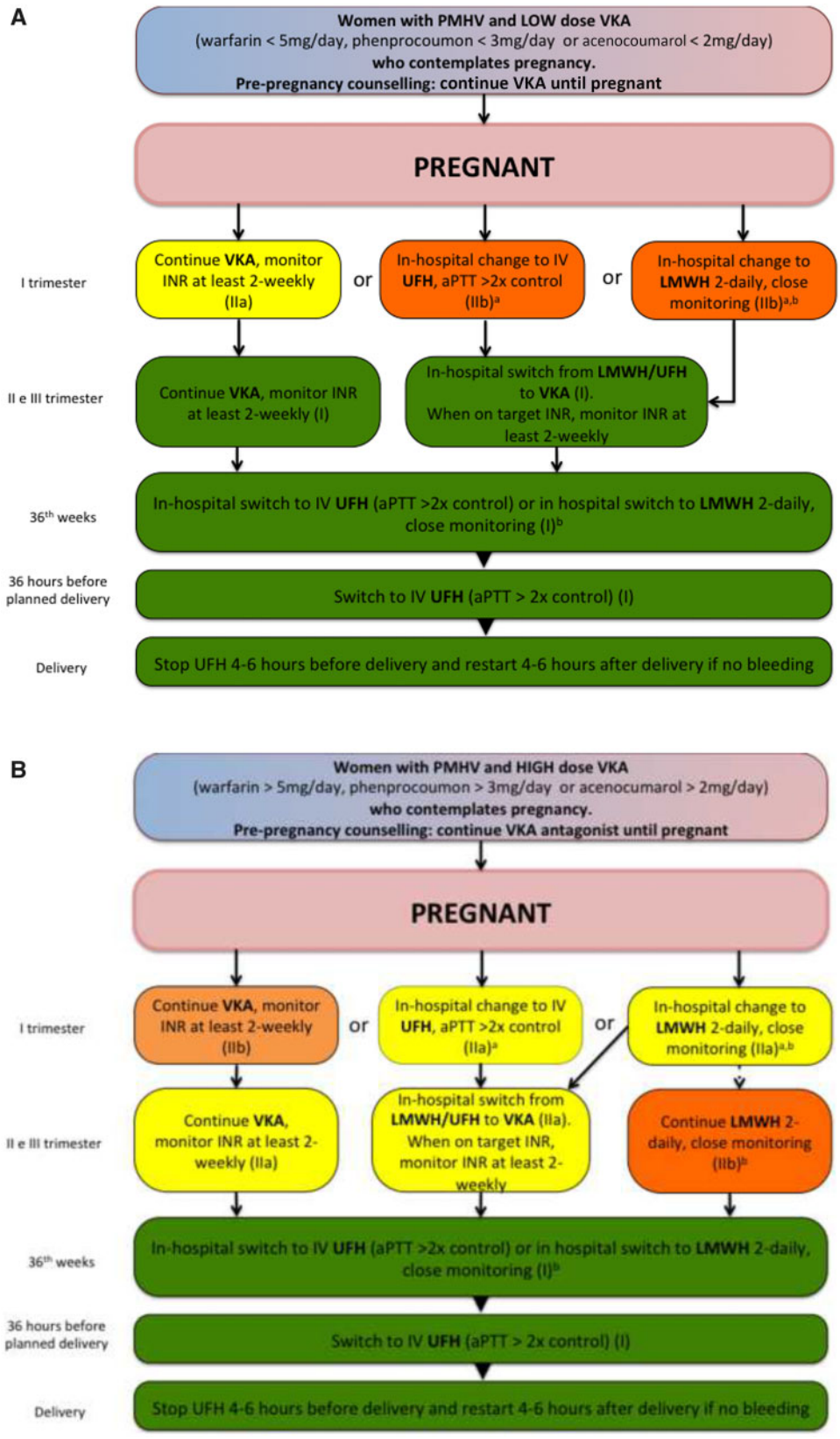

Figure 1 Suggested anticoagulation strategy for women with a prosthetic mechanical heart valve and (*A*) low-dose pre-conception vitamin K antagonist or (*B*) high-dose pre-conception vitamin K antagonist (from Egidy Assenza G, Dimopoulos K, Budts W, Donti A, Economy KE, Gargiulo GD, Gatzoulis M, Landzberg MJ, Valente AM, Roos-Hesselink J. Management of acute cardiovascular complications in pregnancy. See pages 4224–4240).

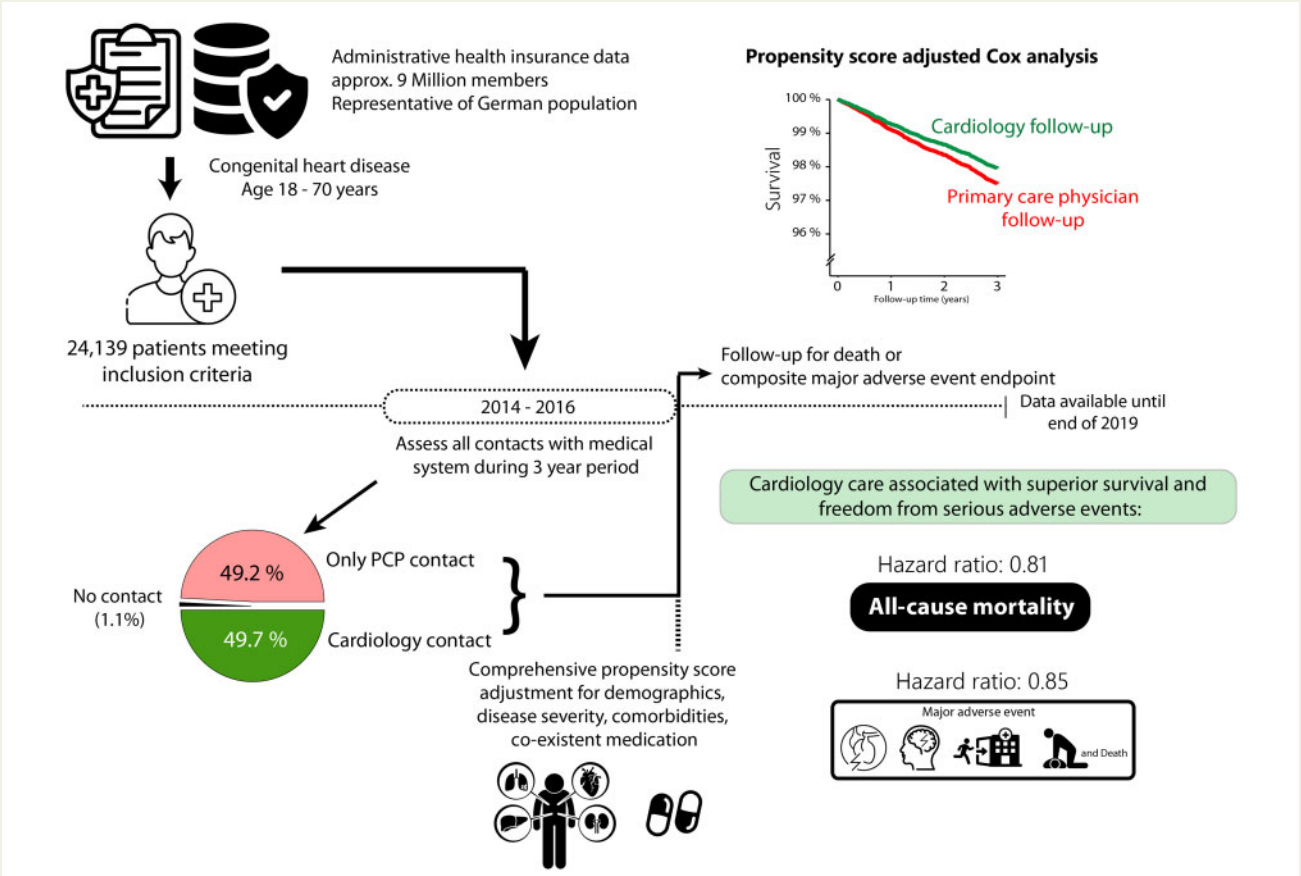

Figure 2 Graphical Abstract (from Diller GP, Orwat S, Lammers AE, Radke RM, De-Torres-Alba F, Schmidt R, Marschall U, Bauer UM, Enders D, Bronstein L, Kaleschke G, Baumgartner H. Lack of specialist care is associated with increased morbidity and mortality in adult congenital heart disease: a population-based study. See pages 4241–4248).

moderate/severe complexity lesions under the care of PCPs compared with those under cardiology follow-up (*Figure 2*).

The authors conclude that cardiology care compared with primary care is associated with superior survival and lower rates of major complications in ACHD. It is alarming that even in a high-resource setting with well-established specialist ACHD care, ∼50% of contemporary ACHD patients are still not linked to regular cardiac care. Thus, more efforts are required to alert PCPs and patients to appropriate ACHD care. The manuscript is accompanied by an **Editorial** by Anne Marie Valente from the Brigham and Women's Hospital in Boston, MA, USA and Abigail Khan from the Oregon Health and Science University in Portland, OR, USA.[13] The authors conclude that it is clear that cardiology care matters for adults living with CHD. The next step for us all is to take this message forward, educating providers, empowering patients, and developing better care networks to support this growing population of individuals with complex care needs.

In a Clinical Research article entitled '**Maternal and neonatal complications in women with congenital heart disease: a nationwide analysis**', Astrid Elisabeth Lammers from the University Hospital Münster in Germany, and colleagues provide population-based data on maternal and neonatal complications and outcome in pregnancies of women with congenital heart disease (CHD).[14] Based on administrative data from one of the largest German Health Insurance Companies (BARMER GEK, ∼9 million members representative for Germany), all pregnancies in women with CHD between 2005 and 2018 were analysed. In addition, an age-matched non-CHD control group was included for comparison, and the association between ACHD and maternal or neonatal outcomes was investigated. Overall, 7512 pregnancies occurred in 4015 women with CHD. The matched non-CHD control group included 6502 women with 11 225 pregnancies. Caesarean deliveries were more common in CHD patients (40.5% vs. 31.5% in the control group; $P < 0.001$). There was no excess mortality. Although the maternal complication rate was low in absolute terms, women with CHD had a significantly higher rate of stroke, HF, and cardiac arrhythmias during pregnancy (P <0.001 for all). Neonatal mortality was low but also significantly higher in the ACHD group (0.83% vs. 0.22%; P = 0.001), and neonates to CHD mothers had significantly low/extremely low birth weight or extreme immaturity, or required resuscitation and mechanical ventilation more often compared with non-CHD offspring. On multivariate logistic regression, maternal defect complexity, arterial hypertension, HF, prior fertility treatment, and anticoagulation with vitamin K antagonists emerged as significant

predictors of adverse neonatal outcome. Recurrence of CHD was 6.1 times higher in infants to ACHD mothers compared with controls.

The authors conclude that this population-based study illustrates a reassuringly low maternal mortality rate in a highly developed healthcare system. Nevertheless, maternal morbidity and neonatal morbidity/mortality were significantly increased in women with ACHD, highlighting the need for specialized care and pre-pregnancy counselling. This manuscript is accompanied by an **Editorial** by Jolien W. Roos-Hesselink from Erasmus MC in Rotterdam, the Netherlands, and colleagues.[15] The authors note that the study by Lammers *et al.* is an excellent and clinically relevant contribution to the existing literature on pregnancy in women with CHD. The study shows that a good healthcare system, a multidisciplinary approach, and decisive pre-pregnancy counselling are effective in achieving safe pregnancies. Pre-pregnancy counselling with an individualized approach is a crucial step in this process, because both maternal and perinatal outcomes vary largely by the complexity of maternal illness, and further studies dedicated to specific congenital diagnoses are still warranted.

Left ventricular non-compaction (LVNC) cardiomyopathy is a devastating genetic disease caused by insufficient consolidation of ventricular wall muscle that can result in inadequate cardiac performance.[16] Despite being the third most common cardiomyopathy, the mechanisms underlying the disease, including the cell types involved, are poorly understood. In a Translational Research article entitled '**Endocardial/endothelial angiocrines regulate cardiomyocyte development and maturation and induce features of ventricular non-compaction**', Siyeon Rhee from Stanford University in Stanford, CA, USA, and colleagues aimed to identify candidate angiocrines expressed by endocardial and endothelial cells in embryonic hearts of Tie2Cre;Ino80$^{fl/fl}$ transgenic mouse (an experimental model of LVNC). Then they tested the effect of these candidates on cardiomyocyte proliferation and maturation.[17] The authors observed a pathological endocardial cell population in non-compacted hearts and identified multiple dysregulated angiocrine factors that dramatically affected cardiomyocyte behaviour. They identified Col15a1 as a coronary vessel-secreted angiocrine factor, down-regulated by Ino80 deficiency, that functioned to promote cardiomyocyte proliferation. Furthermore, mutant endocardial and endothelial cells up-regulated expression of secreted factors, such as Tgfbi, Igfbp3, Isg15, and Adm, which decreased cardiomyocyte proliferation.

The authors conclude that these findings support a model where coronary endothelial cells normally promote myocardial compaction through secreted factors, but that endocardial and endothelial cells can secrete factors that contribute to non-compaction under pathological conditions. The contribution is accompanied by an **Editorial** by Stefanie Dimmeler and Julian Wagner from the Goethe University in Frankfurt, Germany.[18] The authors note that the study by Rhee *et al.* elegantly identifies the importance of a timely orchestrated and well-balanced repertoire of extracellular factors that coordinate the proper development of the left ventricle. It will be important to learn more about the cellular cross-talk to understand the mechanisms of cardiac development and homeostasis. The interplay between endothelial cells and other vascular cells such as pericytes and smooth muscle cells, and fibroblasts and immune cells, with cardiomyocytes has to be taken into account. The modulation of extracellular matrix proteins and paracrine factors may also be a therapeutic strategy promoting cardiac repair and regeneration, but probably needs to be carefully adapted to the underlying stage and type of heart disease.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled **'Big cohort studies offer insights into preventable risk factors'**, Karolina Agnieszka Wartolowska and Alastair John Stewart Webb from the John Radcliffe Hospital in Oxford, UK comment on the recent Editorial '**On cerebrotoxicity of antihypertensive therapy and risk factor cosmetics**' by Franz H. Messerli from the University of Bern in Switzerland.[19,20] Messerli *et al.* respond in a separate comment.[21]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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