Table S1. Background for statements presentation

Statements		Background	
		Summary of survey* results as basis of the topics addressed	Selection and framing of statements
Considerations for optimal ACE-I dosage			
1	There is a need for clear monitoring schedules for the early detection of acute kidney injury in paediatric patients on ACE-I therapy.	• 25% of participants reported not following any specific criterion to decide when to stop increasing ACE-I dose and/or withdraw therapy when deterioration of the renal function is detected. • Disparity in the cut-off values selected by those that base decisions on a formal limit. • Only 29 out of 100 participants reported following a formal blood pressure cut-off value to decide when to withdraw ACE-I if hypotension develops in the context of the therapy.	Little specific guidance has been published (Kantor et al. 2013, Taketomo, Hodding and Kraus 2014), poor description of criteria followed in most of paediatric heart failure studies.
2	There is a need for clear blood pressure cut off points for decision making when up-titrating the dose of ACE-I in paediatric patients.		
3a	In the ACE-I dose up-titration phase daily dose should NOT be increased at less than 48h intervals.	• Wide variability in the starting and maintenance ACE-I doses in use reported to treat heart failure in children.	Due to the complexity of the topic, discussion about adequate dosing schedules of the different ACE-I in the different age groups was out of the scope of this study. We identified two general criteria that might serve as staring points in the achievement of standard dosing criteria. The supplement table of the paediatric guideline elaborated by the Canadian Cardiovascular Society (Kantor et al. 2013) recommends increasing the captopril dose every 48h. This is the shortest suggested interval we identified in the literature for ACE-I up-titration in paediatric patients with heart failure. The ESC guideline for the management of heart failure in adults (McMurray et al. 2012 supplementary information: McMurray et al. 2005) recommends doubling the dose at each step during up-titration in the therapy of heart failure.
3b	In the ACE-I dose up-titration phase the optimal way to proceed is to double the dose at each up-titration step.		

Statements		Background	
		Summary of survey* results as basis of the topics addressed	Selection and framing of statements
4	If deterioration of the renal function occurred in a patient on ACE-I therapy, concomitant diuretic medication should be readjusted before deciding to down titrate/ stop up-titrating the ACE-I.	• Participants repeatedly commented on the influence of concomitant diuretic therapy in the strategy to be best adopted when deterioration of renal function develops in the context of ACE-I.	ESC guideline for the management of heart failure in adults (McMurray et al. 2012 supplementary information: McMurray et al. 2005) recommends considering first reducing the dose of diuretics, if no signs of congestion exist, when deterioration of renal function is detected in patients on ACE-I.
5	If no adverse events occur, ACE-I dose should be increased to the target dose, even if the patient has already experienced improvement with a lower dose.	• Division of opinion on how to establish optimal ACE-I maintenance dose: 42% aim for target dose, 45% stop when improvement is observed.	ESC guideline for adults recommends aiming "for target dose or, failing that, the highest tolerated dose" (McMurray et al. 2012 supplementary information: McMurray et al. 2005). These target doses are those that were used and showed an improvement in survival and hospitalizations in key randomized trials. Evidence in adults suggests that clinical symptoms appear to be inadequate in determining optimal ACE inhibitor dose level (López-Sendón et al. 2004)
6	In order to maximise the accuracy of the ACE-I dose given, the use of different types of formulations for a patient throughout the duration of the treatment should be avoided.	• Half (47%) of the respondents indicated that the ACE-I formulations they prescribe are provided to their patients from more than a single source.	As no licensed paediatric appropriate formulation is commercialised in Europe, pharmacies provide formulations individually prepared for the patients under prescription. It has been documented that a wide variety of unlicensed and untested ACE-I formulations, with no proven bioequivalence, are used interchangeably in Europe (Mulla et al. 2007, Pabari et al. 2012). Sometimes parents have to crush tablets and dissolve or disperse them for administration to their child. It is not possible to be confident that the rate and extent of ACE-I absorption do not vary according to its formulation.

Statements		Background	
		Summary of survey* results as basis of the topics addressed	Selection and framing of statements
ACE-I for the management of congenital heart diseases			
7	Paediatric patients with asymptomatic mitral or aortic regurgitation benefit from ACE-I therapy	• 92 of the participating physicians reported using ACE-I to treat patients with valve regurgitation; 33 treat only symptomatic patients, 44 both symptomatic and asymptomatic and 15 reported using them only for asymptomatic patients. In summary, approximately one third of these participants reported not using ACE-I to treat asymptomatic patients with valve regurgitation.	Hemodynamic benefits of ACE-I have been observed in children with valve regurgitation in some small experimental studies (Alehan et al. 1997, Calabro et al. 1999, Mori et al. 2000), all of which included only patients with no heart failure symptoms.
8	Paediatric patients with pressure overload lesions should be routinely prescribed ACE-I.	• Half of the participants reported using ACE-I in the context of pressure overloading lesions.	ISHLT Practice Guidelines for Management of Heart Failure in Children (Rosenthal et al. 2004) stated "In pressure-induced left ventricular hypertrophy, with normal myocardial function, ACE inhibitors are not recommended in the absence of a non-cardiac indication such as hypertension. (Level of Evidence C; Strength of Recommendation III)". The appropriateness of treating patients with pressure overloading lesions such as aortic stenosis with drugs acting in the renin-angiotensin-aldosterone-system in has been debated. Concerns about the potential risks have prevented the widespread use of ACE-I to treat concomitant hypertension in this context, however evidence in adults suggests these concerns are largely unfounded (Cox et al. 1998, Marquis-Gravel et al. 2016)
9	ACE-I therapy should NOT be routinely instituted for all patients with single ventricle congenital heart disease, but could be considered in specific cases such as in situations of valve regurgitation or ventricular dysfunction.	• 84% of the survey participants reported using ACE-I to treat symptomatic and/or asymptomatic patients with single ventricle congenital heart diseases.	The only large randomized controlled trial published testing the effects of ACE-I in children with single ventricle concluded their results did "not support the routine use of enalapril in this population" (Hsu et al. 2010). Other small experimental studies (Kouatli et al. 1997, Lee et al. 2011) also failed to prove any benefit. ISHLT 2014 guideline (Kirk et al. 2014) recommendation in this regard*:* "ACE-I therapy should not be routinely instituted for all patients with single ventricle congenital heart disease, but could be considered in specific cases such as in situations of valve regurgitation or ventricular dysfunction."

Statements		Background	
		Summary of survey* results as basis of the topics addressed	Selection and framing of statements
Neurohumoral antagonists for the management of heart failure related to dilated cardiomyopathy			
10	If beta-blockers are to be introduced for the management of heart failure, patients should also receive an ACE-I concomitantly.	• 94% of the participants reported using beta-blockers in symptomatic patients. Approximately half of them introduce ACE-I first ad add beta-blockers in a further step if patients remain symptomatic. • 55% of the 89 survey participants that reported prescribing drug treatment to patients with DCM that are asymptomatic choose a therapy that includes a beta-blocker; 29% in a two-drug only combination with an ACE	A Cochrane review of 2016 (Alabed et al. 2016) concluded there is not enough evidence to encourage or discourage their use but existing data suggest that children with congestive heart failure might benefit from treatment with beta-blockers. In adults, beta-blockers are recommended in both symptomatic and asymptomatic patients with heart failure with low ejection fraction, always in combination with an ACE-I. However, benefits in asymptomatic patients without a history of myocardial infarction are less clear and recommendations not uniform (Mc Murray et al. 2012, Yancy et al. 2013). Paediatric guidelines have adopted similar recommendations in the absence of definitive paediatric data (Kantor et al. 2013; Kirk et al. 2014).
11	Beta-blockers should be considered for the management of patients with heart failure in asymptomatic stages.		
12	Aldosterone antagonists should only be introduced for patients with persisting symptoms despite treatment with ACE-I (+/- beta-blocker).	• 61% of the participants reported starting the therapy of symptomatic DCM patients with a drug regimen based on an ACE-I and an aldosterone antagonist.	Aldosterone antagonists have proven to have a positive impact in terms of survival and hospitalizations reduction in adults with heart failure when used at low doses (below those prescribed when used with diuretic purposes). ESC guidelines for the management of heart failure in adult patients (McMurray et al. 2012) recommend the use of aldosterone antagonists "for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤ 35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker". No evidence exists in this regard for children, but the Canadian Cardiovascular Society has integrated this recommendation into their paediatric guideline (Kantor et al. 2013). The ISHLT guideline says, "it is reasonable to consider aldosterone antagonists in children", but is no concrete about timing of introduction (Kirk et al. 2014).
13	Paediatric validated scores for heart failure severity staging should be connected with pharmacotherapeutic recommendations in further guidelines.	• Only half of the physicians questioned reported making use of clinical scores to evaluate the effectiveness of the therapy.	The grading of heart failure signs and symptoms in children remains challenging. Some scores to grade the severity of heart failure in children have been developed (Ross et al. 2012) and even though none of them has been validated yet as surrogate clinical endpoints with large number of patients, neurohormonal activation and deteriorating clinical status have been shown to correlate with increasing class (Hsu and Pearson 2009). However, no standard definitions seem to be routinely applied. ISHLT (Kirk et al. 2014) and Canadian (Kantor et al. 2013) paediatric guidelines on heart failure management apply also self-developed and adult-adapted scales when making recommendations of therapy by heart failure stage.

* A Europe-wide survey on the pharmacological management of paediatric heart failure was conducted between January and May 2015. Hundred paediatricians dedicated to cardiology, representing 100 different hospitals in 27 European countries participated: Castro Díez C, Khalil F, Schwender H, Dalinghaus M, Jovanovic I, Makowski N, Male C, Bajcetic M, van der Meulen M, de Wildt SN., Ablonczy L, Szatmári A (†), Klingmann I, Walsh J, Läer S. Pharmacotherapeutic management of paediatric heart failure and ACE-I use patterns: a European survey. Submitted 1st October 2018 to BMJ Paediatrics Open.

References

Alabed S, Sabouni A, Al Dakhoul S, *et al.* Beta-blockers for congestive heart failure in children. *Cochrane Database Syst Rev* 2016;:CD007037. doi:10.1002/14651858.CD007037.pub3

Alehan D, Ozkutlu S. Beneficial effects of 1-year captopril therapy in children with chronic aortic regurgitation who have no symptoms. *Am Heart J* 1998;**135**:598–603.

Calabrò R, Pisacane C, Pacileo G, *et al.* Hemodynamic effects of a single oral dose of enalapril among children with asymptomatic chronic mitral regurgitation. *Am Heart J* 1999;**138**:955–61.

Cox NL, Abdul-Hamid AR, Mulley GP. Why deny ACE inhibitors to patients with aortic stenosis? Lancet. 1998 Jul 11;352(9122):111-2.

Hsu, Pearson GD. Heart failure in children: part I: history, etiology, and pathophysiology. *Circ Heart Fail* 2009;**2**:63–70. doi:10.1161/CIRCHEARTFAILURE.108.820217

Hsu, Zak V, Mahony L, *et al.* Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation* 2010;**122**:333–40. doi:10.1161/CIRCULATIONAHA.109.927988

Kantor PF, Lougheed J, Dancea A, *et al.* Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. *Can J Cardiol* 2013;**29**:1535–52. doi:10.1016/j.cjca.2013.08.008

Kirk R, Dipchand AI, Rosenthal DN, *et al.* The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. [Corrected]. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 2014;**33**:888–909. doi:10.1016/j.healun.2014.06.002

Kouatli AA, Garcia JA, Zellers TM et al. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation. 1997 Sep 2;96(5):1507-12.

Lee KJ, Yoo SJ, Holtby H, et al. Acute effects of the ACE inhibitor enalaprilat on the pulmonary, cerebral and systemic blood flow and resistance after the bidirectional cavopulmonary connection. Heart. 2011 Aug;97(16):1343-8. doi: 10.1136/hrt.2011.225656. Epub 2011 Jun 5.

López-Sendón J, Swedberg K, McMurray J, *et al.* Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The Task Force on ACE-inhibitors of the European Society of Cardiology. *Eur Heart J* 2004;**25**:1454–70. doi:10.1016/j.ehj.2004.06.003

McMurray J, Cohen-Solal A, Dietz R, at al. Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail. 2005 Aug;7(5):710-21.

Marquis-Gravel G, Redfors B, Leon MB1, Généreux P. Medical Treatment of Aortic Stenosis. Circulation. 2016 Nov 29;134(22):1766-1784.

McMurray J, Adamopoulos S, Anker SD, et al.; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012 Jul;33(14):1787-847. doi: 10.1093/eurheartj/ehs104. Epub 2012 May 19.

Mori Y, Nakazawa M, Tomimatsu H, *et al.* Long-term effect of angiotensin-converting enzyme inhibitor in volume overloaded heart during growth: a controlled pilot study. *J Am Coll Cardiol* 2000;**36**:270–5

Mulla H, Tofeig M, Bu'Lock F, *et al.* Variations in captopril formulations used to treat children with heart failure: a survey in the United kingdom. *Arch Dis Child* 2007;**92**:409–11. doi:10.1136/adc.2006.109389

Pabari RM, McDermott C, Barlow J, *et al.* Stability of an alternative extemporaneous captopril fast-dispersing tablet formulation versus an extemporaneous oral liquid formulation. *Clin Ther* 2012;**34**:2221–9. doi:10.1016/j.clinthera.2012.10.005

Rosenthal D, Chrisant MRK, Edens E, et al. International Society for Heart and Lung Transplantation: Practice guidelines for management of heart failure in children. The Journal of Heart and Lung Transplantation 2004;23:1313-33.

Ross RD. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. *Pediatr Cardiol* 2012;**33**:1295–300. doi:10.1007/s00246-012-0306-8

Taketomo C, Hodding J, Kraus D. *Pediatric & Neonatal Dosage Handbook*. 21st ed. Hudson, Ohio: : Lexi-Comp, Inc 2014.

Yancy CW, Jessup M, Bozkurt B, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;**128**:1810–52. doi:10.1161/CIR.0b013e31829e8807