Cardiology in the Young

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Pharmacotherapy in paediatric heart failure: a Delphi process

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Abstract

Background: Little evidence exists to support pharmacotherapeutic strategies for heart failure management in paediatrics. A recent Europe-wide survey suggests that this translates into substantial variability in clinical practice. *Objective:* To conduct a formal discussion among an expert group of paediatric cardiology physicians on controversial aspects regarding the pharmacotherapy of children heart failure, facilitate consensus, and highlight areas of agreement and disagreement. *Methods:* A two-round modified Delphi process was conducted between July and August 2015. Topics addressed were predominantly selected from the results of a previous Europe-wide survey. Fourteen statements were presented for discussion grouped under three categories; Angiotensin-converting-enzyme-inhibitors: Considerations for optimal dosage; Angiotensin-converting-enzyme-inhibitors for the management of CHDs; Neurohumoral antagonists for the management of dilated cardiomyopathy-related heart failure. *Results:* A total of 13 paediatricians dedicated to cardiology from across Europe and the United States of America completed the study; of them, 92% had a working experience in the field of more than 10 years and were working in a specific paediatric cardiology unit. Agreement on the acceptance/rejection of 11 statements was achieved. Results show agreement on the importance of a set of topics relevant to the standardisation of the therapy as well as consensus upon specific therapeutic attitudes. *Conclusions:* We have found areas of common thinking and motivation, which can provide a means of triggering scientific collaboration. Our results might also contribute to disseminate available paediatric evidence and promote reducing unjustified variability in everyday practice. Until solid evidence is available, other research methods can contribute to advancing the goal of safe and effective paediatric heart failure pharmacotherapy.

Pharmacotherapeutic strategies for the management of paediatric heart failure are largely supported by extrapolation of adult data and clinician expertise. Therefore, the prescribing of unlicensed and off-label drugs is predominant in this setting.[1–3] A recent Europe-wide survey suggests that this translates into substantial variability in clinical practice. This lack of standardisation is a potential threat to the safety and quality of the medical care provided.[4,5]

It is well known that conducting randomised clinical trials in the paediatric heart failure population poses many challenges and is often not possible.[6,7] Hence it is vital to consider alternative approaches to achieve safe and effective therapy. In this regard, the potential of qualified opinion has been underused, with few structured debates and expert consensus documents having been published. However, insights of experts on an issue can be a valuable contribution for decision-making when evidence is scarce or contradictory.[8–10]

The Delphi technique is a method to enable structured group discussions and has previously been used in other fields of healthcare research.[8,9,11–13] It is a means of "eliciting and refining group judgements" and "obtaining the most reliable consensus of opinion"[14] that is based on the assumption that group opinion is more valid than individual opinion when the issue is one where exact knowledge is not available.[13] The key features of the method are the anonymity between participants with controlled feedback provided in a structured manner.[15] It allows the inclusion of individuals across diverse locations while minimising the main shortcomings of traditional consensus methods: the influence of dominant individuals, irrelevant communications, and group pressure.[16]

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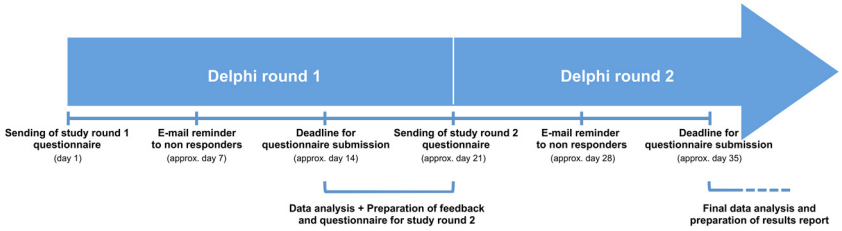


Figure 1. Study timeline.

The study presented here was conducted as part of the European Commission funded "Labelling of Enalapril from Neonates to Adolescents" project (https://www.lena-med.eu). Our aim was to conduct a formal discussion, using the Delphi technique, among an expert group of paediatric cardiology physicians, on controversial aspects regarding the pharmacological management of children with heart failure which had been predominantly identified through a previous Europe-wide survey. Special focus was placed on angiotensin-converting-enzyme-inhibitors. The intention was to gain an understanding of the experts' opinions, encourage debate, facilitate consensus, and highlight areas of agreement and disagreement.

Materials and methods

Overall study design

The study was designed taking into consideration relevant literature on Delphi research methodology and publications applying this technique to health science research.[8,11–13,15,17–21] A two-round modified Delphi process design was chosen,[17,19] whereby the panel of experts was given pre-selected items upon which to make a judgement.[13] This approach enables a greater efficiency in use of time than the traditional Delphi process, whilst reducing the risk of dropouts, and has been used extensively by others.[8,12,20,22–24]

Expert panel recruitment

The aim was to recruit an expert panel comprising 10–15 paediatricians with experience in the field of cardiology, preferably with representation of the four European geographical regions.[8,9,21,25–27] Non-European experts were also considered. This panel size has been regarded as appropriate for Delphi processes where topics covered require experts with very specific knowledge.[8,9,21,25–27] Physicians who had participated in the "European survey on the pharmacological management of paediatric heart failure", or those known by the investigators via personal contact who were considered qualified for their knowledge and interest in the topic, were invited to participate via e-mail. Those invitees expressing their willingness to participate and who were available on the study dates participated in the study and formed the expert panel.

Questionnaire design and administration

Recommendations on survey and questionnaire design best practice were followed.[13,28,29] Topics for the discussion were predominantly selected from areas of controversy identified in the "European Survey on the management of paediatric heart failure" – the paper where the results of this survey have been reported is available on open access in BMJ Paediatrics Open. The rationale for the selection of the contents is provided in Supplementary Table S1. These controversial topics were framed as statements – either affirmative or negative – containing a professional judgement or a clinical recommendation on any aspect of paediatric heart failure drug therapy. Participants were asked to rate their level of agreement with the survey statements by using 5-point Likert scales, the use of which is widely accepted.[8,12,20,30] Each answer category was presented with a verbal label and a numeric descriptor: 1 = Strongly disagree, 2 = Disagree, 3 = Neither agree nor disagree, 4 = Agree, 5 = Strongly agree. A free text field in which participants could enter rationale and/or further comments to their answers accompanied each statement. Fourteen statements grouped under three categories were presented; Angiotensin-converting-enzyme-inhibitors: Considerations for optimal dosage; Angiotensin-converting-enzyme-inhibitors for the management of CHDs; Neurohumoral antagonists for the management of heart failure related to dilated cardiomyopathy. In addition, three demographic questions were posed. The questionnaire was peer reviewed at the investigators site. A pilot test was not deemed necessary since the questionnaire was largely based on a previously tested survey. Furthermore, wording from recognised guidelines was adopted when possible.

Prior to the beginning of the study, participants received written information about Delphi methodology and guidance on how to complete the process. The web-survey platform EvaSys® version 6.1 was used for the administration of the questionnaire, which was selected for its compliance with the European Union Data Protection Directive 95/46/EC. An individualised link to the questionnaire was sent by e-mail together with instructions on how to navigate through the survey. In the second study round, the experts were asked to re-evaluate those statements on which consensus had not been reached after the first round. Quantitative and qualitative feedback on the first round results accompanied each statement: a summary of Likert score rating, consensus evaluation, and rationale provided by participants supporting their responses.[21,31] The participants' own rating given to the statement in the previous round was not presented as part of the feedback.[17] Additionally, the participants were provided with information – background or supporting evidence to statements – that could be relevant to facilitate the discussion. The identity of the experts in the panel remained unknown to one another throughout the study duration. A complete copy of the questionnaire can be found in Supplementary Figure S1. The study timeline is presented in Figure 1.

Data collection, analysis, and interpretation

Data were collected between July and August 2015. To minimise errors during data processing, data extraction from the EvaSys® platform and preparation of ready-to-analyse data were conducted by two researchers independently, and the results were checked for consistency. Data analysis was performed with R® version 3.2.3 and R-Studio® version 099.465. Charts presented in this manuscript were created in Excel® v.16.10.

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		Statement	Evaluation on the 5-point Likert scale				Consensus (round)
			% panellist disagreeing	% panellists agreeing	Mean	(95% CI)	
ACE-I: Considerations for optimal 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.	15.4	69.2	4.00	(3.37 – 4.63)	Yes (1)
	2	There is a need of clear blood pressure cut off points for decision making when up-titrating the dose of ACE-I in paediatric patients.	7.7	76.9	4.00	(3.50 – 4.50)	Yes (1)
	3a	In the ACE-I dose up-titration phase daily dose should NOT be increased at less than 48h intervals.	7.7	84.6	3.92	(3.51–4.33)	Yes (2)
	3b	In the ACE-I dose up-titration phase the optimal way to proceed is to double the dose at each up-titration step.	46.2	46.2	3.15	(2.49-3.81)	No
	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.	15.4	76.9	3.62	(3.05-4.19)	Yes (2)
	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.	38.5	46.2	3.23	(2.49-3.97)	No
	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.	15.4	76.9	3.85	(3.19-4.51)	Yes (2)
ACE-I for the management of CHD	7	Paediatric patients with asymptomatic mitral or aortic regurgitation benefit from ACE-I therapy	15.4	76.9	3.69	(3.23-4.15)	Yes (2)
	8	Paediatric patients with pressure overload lesions should be routinely prescribed ACE-I.	69.2	15.4	1.92	(1.27-2.57)	Yes (1)
	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.	15.4	84.6	4.00	(3.33-4.67)	Yes (1)
Neurohumoral antagonists for the management of DCM-related HF	10	If beta-blockers are to be introduced for the management of heart failure, patients should also receive an ACE-I concomitantly.	7.7	84.6	4.15	(3.66-4.64)	Yes (1)
	11	Beta-blockers should be considered for the management of patients with heart failure in asymptomatic stages.	15.4	69.2	3.69	(3.18 – 4.2)	Yes (1)
	12	Aldosterone antagonists should only be introduced for patients with persisting symptoms despite treatment with ACE-I (+/- beta-blocker).	46.2	53.8	3.23	(2.56-3.90)	No
	13	Paediatric validated scores for heart failure severity staging should be connected with pharmacotherapeutic recommendations in further guidelines.	7.7	84.6	4.00	(3.56 – 4.44)	Yes (1)

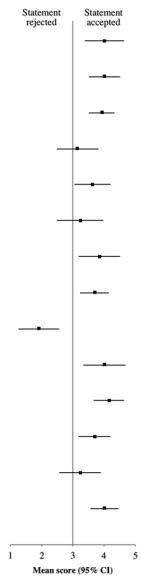


Figure 2. Global results of the Delphi process. Likert scale: 1 = Strongly disagree, 2 = Disagree, 3 = Neither agree nor disagree, 4 = Agree, 5 = Strongly agree. ■ Mean 5-point Likert scale score. ACE-I, angiotensin-converting-enzyme-inhibitor; CHD, congenital heart diseases; CI, confidence interval; DCM, dilated cardiomyopathy; HF, heart failure.

The level of consensus among experts on each of the statements to be judged was evaluated by calculating the mean 5-point Likert scale score and the corresponding 95% confidence interval after each study round. Consensus was defined as follows: [8,12,20]

- Upper bounder of confidence interval <3: consensus exists among experts that a statement is false.
- Lower bounder of confidence interval >3: consensus exists among experts that a statement is true.
- Confidence interval includes the 3: no consensus exists among experts on whether a statement is or not true.

Ethics approval

This study was conducted in compliance with the European Union Data Protection Directive 95/46/EC and was approved by Institutional Ethics Committee and Data Protection Officer at the Heinrich-Heine-University Düsseldorf, Germany. Electronic informed consent was obtained from each participant via the EvaSys® platform.

Results

Study population

A total of 37 paediatricians with experience in the field of cardiology were invited to participate in the study. Of the 14 that agreed to take part, one did not return the completed questionnaire within the pre-established deadline in the first study round and was therefore excluded from the study; the remaining 13 physicians completed both rounds of the Delphi process and were finally considered for analysis. Experts from Austria (1), Belgium (1), Bosnia and Herzegovina (1), France (1), Germany (3), Greece (1), the Netherlands (1), Russia (1), Serbia (1), the United Kingdom (1), and the United States of America (1) participated. All four geographical regions of Europe were represented. Of the 13 participants, 12 had a working experience in the field of paediatric cardiology of more than 10 years; the remaining one participant had experience of between 5 and 10 years. All the physicians but one worked in a specific paediatric cardiology unit; the latter had retired but had 35 years' experience of working in a university hospital.

Results of the Delphi process

Overall, after the two rounds of questions, agreement on 11 of the 14 statements presented for discussion (79%) was achieved according to the pre-established criteria. In the first round of the process, consensus on 7 of the 14 statements was achieved, with six being accepted and one rejected. In the second study round, consensus on four further statements was achieved (all accepted). Agreement on the three remaining statements was not reached due to polarisation of opinions for and against the veracity of the phrases. Detailed global results – evaluation of statements on the 5-point Likert scale and the corresponding statistics – are presented in the table and in Figure 2. Figure 3 shows the distribution of opinions in the first and second study rounds on the four statements, upon which consensus was reached in the second study round.

Discussion

A series of controversial aspects relating to paediatric heart failure therapy has been discussed in this Delphi study, and the opinions of an international group of 13 physicians with experience in the field of paediatric cardiology are reflected in this document. The expert panel showed consensus in their professional judgement on 11 of the 14 statements presented for discussion according to the pre-established criteria.

Statements upon which consensus was achieved highlight areas where closer views and common interests exist among the experts consulted. Some of those statements point to topics relevant to the standardisation of the therapy that the panel agreed were of importance: developing guidance on the approach towards adverse events in the context of angiotensin-converting-enzyme-inhibitors therapy, promoting the correlation of paediatric validated scores with therapeutic recommendations in further guidelines, and

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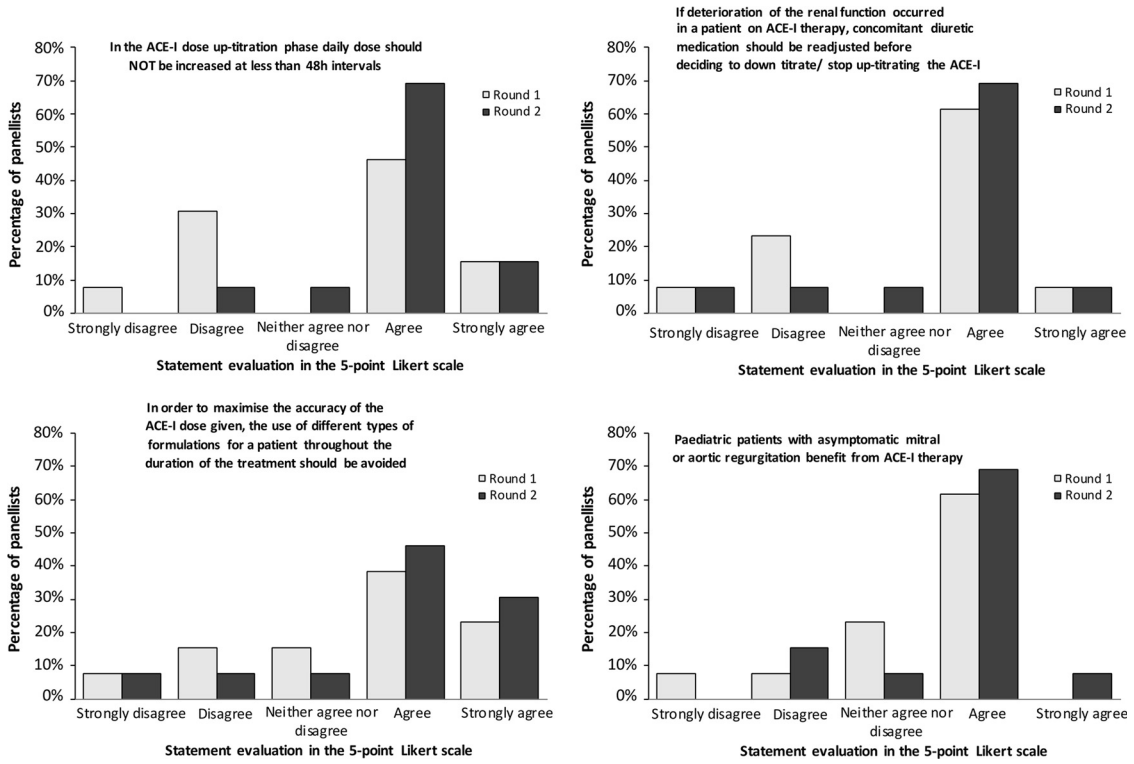


Figure 3. Statements upon which consensus was reached in the second study round scored in the 5-point Likert scale in the Delphi process rounds 1 and 2. ACE-I, angiotensin-converting-enzyme-inhibitor.

reducing heterogeneity associated with unlicensed angiotensin-converting-enzyme-inhibitors formulations.

Hypotension and deterioration of renal function are the most frequently reported adverse events related to angiotensin-converting-enzyme-inhibitors in paediatric heart failure patients.[32] However, no standardised criteria on how to best monitor patients or define critical cut-off values exist, and few specific recommendations for problem-solving when these adverse events occur have been published.[2,33] Results of our previous survey indicate that paediatric patients are being subjected to variable approaches for managing these aspects (Supplementary Table S1). The results of the Delphi process showed agreement among the expert panel in the need to fill this gap (statements 1 and 2). While it is true that current paediatric data do not allow the generation of definitive recommendations, paediatric heart failure societies and working groups may be motivated to develop guidance that compiles the best knowledge available, to facilitate a standardised approach to therapy.

Agreement was also achieved on the relevance of linking treatment algorithms to validated paediatric heart failure severity scores (statement 13), which is not yet a standard. The use of self-developed or adult-adapted grading systems is frequent,[2,3] and it seems that division of opinion exists among European paediatricians about their usefulness in everyday practice (Supplementary Table S1). Accurate grading of heart failure severity in children remains challenging, and paediatric-specific scoring systems that have been developed require further validation.[34–37] However, despite limitations, promoting as far as possible the use of uniform paediatric-adapted definitions seems essential to move heart failure therapy into the realm of evidence-based medicine. This would facilitate the correct application of guideline recommendations, the evaluation of therapy-related outcomes, and the interpretation and performance of further research.

The results may also contribute to raising awareness of the potential consequences of the interchangeable use of different angiotensin-converting-enzyme-inhibitor formulations. The panel agreed on the importance of discouraging this practice (statement 6). It has been documented that unlicensed and manipulated preparations that are used to overcome the absence of licensed paediatric medicines are heterogeneous and may not be bioequivalent.[38,39] Inconsistency in the rate and extent of absorption is likely to exist, and this may for example influence outcomes and cause variability in the duration of time needed to optimise therapy. In addition, the use of manipulated dosage forms can lead to inaccurate dosing. It is likely that many paediatric patients across Europe are exposed to this potential variability (Supplementary Table S1). This may also have an impact on the interpretation of published angiotensin-converting-enzyme-inhibitor efficacy and safety data, where information on the drug formulation and its administration is often not reported. The panel judgement supports the idea that the marketing of age-appropriate formulations would be beneficial.

The results also show specific therapeutic attitudes upon which consensus was achieved. These statements might trigger the sharing of data that are being recorded on a routine basis in clinical practice to evaluate the outcomes of agreed treatment strategies, which may help confirm their effectiveness and/or define best candidates for therapy. It has been recognised that large observational studies, databases, and registries, when well designed, could represent an alternative means by which to generate the much-needed clinical evidence.[7,40] The agreement on the veracity of these statements might also contribute to the efficient dissemination of relevant paediatric research to the physicians for whom this information is important, which has been found to be an area that needs to be improved.[41,42] Three of these statements considered the role of angiotensin-converting-enzyme-inhibitors in the context of

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CHD. In their judgement, the panel discouraged routine use in patients with pressure overloading lesions (statement 8) and single ventricle physiology (statement 9). Even though the results of our previous survey suggest that the prescribing of angiotensin-converting-enzyme-inhibitors in single ventricle patients is still extensive (Supplementary Table S1), the authors of the Infant Single Ventricle Trial, the only large paediatric randomised controlled trial on angiotensin-converting-enzyme-inhibitors that has been published, concluded that their results did not support the routine use of enalapril in this scenario.[43] The International Society for Heart and Lung Transplantation paediatric guideline recommendation in this regard, which we undertook as statement 9 for discussion, supports this conclusion.[3] In contrast, the panel agreed in the second round of questions that children with valve regurgitation that are asymptomatic may benefit from angiotensin-converting-enzyme-inhibitor therapy (statement 7). Evidence indicates that adult patients with mitral and aortic regurgitation are good candidates for angiotensin-converting-enzyme-inhibitors only if symptoms and/or left ventricular dysfunction exist, and it seems that practice among European paediatricians is largely influenced by this (Supplementary Table S1). Data indicating benefit in paediatrics come from a small randomised controlled trial and several observational studies, all of which included only asymptomatic patients.[44–46] This evidence is limited, but Li et al reported that a perceived lack of equipoise exists among paediatricians, which hinders the conduction of randomised controlled trials in this scenario.[6] Collaboration may contribute to the elucidation of patients' subgroups whom would especially benefit.

The panel also agreed on the two statements regarding the use of beta-blockers in dilated cardiomyopathy-related heart failure. Consensus existed that beta-blockers should be considered in the therapy of asymptomatic children, and that they should be used in combination with an angiotensin-converting-enzyme-inhibitor (statements 10 and 11). In adults, a combination of beta-blocker with an angiotensin-converting-enzyme-inhibitor has proven benefit in asymptomatic patients with left ventricular dysfunction that have a history of myocardial infarction, although advantages when this is not the case are less clear and recommendations are not uniform.[47,48] Paediatric data in this scenario are scarce and a marked division of opinion seems to exist among European paediatricians in this regard (Supplementary Table S1);[49] however, the expert panel judgement supports the potential benefits of this practice.

The three non-consensus statements identified in this Delphi study may provide greater visibility of some aspects of clinical practice which have a high degree of disparity of opinions among physicians. Two of these are directly related to aspects of heart failure treatment that have great potential to influence the long-term benefits of therapy. The first relates to optimal angiotensin-converting-enzyme-inhibitor maintenance dose in paediatrics (statement 5). Some of the experts in the panel agreed that a target dose should be aimed for, while others considered that up-titration should be stopped once improvement is observed. This marked division of opinion is consistent with the results of our previous survey (Supplementary Table S1). Evidence in adults indicates that the efficacy of angiotensin-converting-enzyme-inhibitors in heart failure patients with left ventricular dysfunction in terms of mortality and hospitalisations reduction is closely related to dose level, and that these effects are explained by mechanisms that probably do not play an important role in the control of symptoms.[50] Thus a response-based maintenance dose selection does not seem to be appropriate, and aiming towards the target doses used in pivotal clinical trials, or failing this, towards the highest tolerated dose, is recommended in adults.[47] On the other hand, unlike in adults, in paediatrics the origin of heart failure is very often multifactorial and not limited to ventricular dysfunction.[37] No dose-effectiveness studies in paediatrics have established the existence of a target dose that produces benefits analogous to those that have been observed in adults and difficulties in achieving high angiotensin-converting-enzyme-inhibitor doses in the paediatric population have been reported.[43] Clinicians may consider comparing outcomes in groups of patients treated according different strategies, which may help establish a common criterion to treat paediatric patients in the most effective way. The same approach would apply to the topic addressed in the second of these non-consensus statements, which relates to the timing of introduction of aldosterone antagonists (statement 12). Results of our previous survey (Supplementary Table S1) revealed that aldosterone antagonists are frequently prescribed to children as part of the initial therapy of symptomatic heart failure, perhaps for their potassium sparing diuretic. However, evidence in adults supports the use of low-dose aldosterone antagonists as add-on therapy in patients that remain symptomatic despite initial therapy to reduce mortality and hospitalisations.[47] Data in paediatrics in this regard are lacking. Some subgroups of paediatric patients have a marked poor prognosis, with a 5-year risk of death or cardiac transplantation of around 50%.[51] It would therefore be prudent to maximise available expert knowledge to drive decisions regarding those treatment strategies.

Validity and limitations

The results of a Delphi process are based on a synthesis of the opinions of a group, meaning that from question to question, some of the individual experts would differ with the consensus view. Furthermore, "the existence of a consensus does not mean that the correct answer has been found".[11] A Delphi process is not intended to provide definitive answers but is rather a means of maximising the benefits from having informed panels consider a problem.[10]

No universally agreed guidelines on the use of the Delphi technique exist, but we have followed a thorough procedure for the design of the study and have reported with transparency all relevant methodological aspects. Characteristics of the expert panel members – paediatricians dedicated to cardiology, 92% working in hospital paediatric cardiology units and with more than 10 years of experience in the field with representation of all four regions of Europe – and the lack of dropouts in the second study round are positive indicators of the quality of our study.[19] We asked 37 physicians to participate, assuming that only part of them would be willing or able to do it. The fact that only 35% of them finally agreed to be part of the expert panel does not compromise our study from the methodological point of view. The relevant response rate in a Delphi process, for its potential to bias the results, is that from the second study round with regard to the first round, which in our case was 100%. Even though it cannot be assured that a different group of physicians with expertise in paediatric cardiology would have produced the same results, findings from Duffield and Akins et al "indicate that the response characteristics of a small expert panel in a well-defined knowledge area are stable in light of augmented sampling".[52,53] Therefore, the larger the sample, the narrower the confidence interval determined based on this sample would have become. This implies that when considering our particular data, a larger expert panel would not have led to a different group decision concerning consensus/non-consensus statements.

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This study has the limitations inherent to the Delphi technique.[11] It is also recognised that the study is limited by the simplified manner in which the statements presented for debate addressed topics of great complexity. An exhaustive questionnaire would have required considerable demands of time and effort to the participants, which would have compromised the feasibility of the study. The study participants were selected from different backgrounds to assure that no interest or pre-conceived opinion was likely to dominate. However, it should be noted that one of the participants was directly involved in a study whose results were very relevant to the discussion regarding the pertinence of angiotensin-converting-enzyme-inhibitors in single ventricle patients, and his opinion on that statement was not unexpected. Nevertheless, a different response by this participant would not have changed the global consensus results on that particular statement. Furthermore, one of the expert panel members was researcher in the "Labelling of Enalapril from Neonates to Adolescents" project and had been involved in previous discussions on study-relevant topics.

Conclusions

This Delphi process reflects the opinion of a 13-member expert panel of paediatricians experienced in cardiology. Consensus was achieved on 11 of the 14 statements addressing controversial aspects of paediatric heart failure therapy presented for discussion. Agreement existed on the importance of a set of topics relevant to the standardisation of therapy: developing guidance on the approach towards adverse events in the context of angiotensin-converting-enzyme-inhibitor therapy, promoting the correlation of paediatric validated scores with therapeutic recommendations in further guidelines, and reducing heterogeneity associated with unlicensed angiotensin-converting-enzyme-inhibitors formulations. Agreement was also achieved on discouraging routine use of angiotensin-converting-enzyme-inhibitors in single ventricle physiology and pressure overloading lesions, whereas the panel agreed that children with mitral or aortal regurgitation that are asymptomatic might benefit from therapy and that beta-blockers may be recommended for asymptomatic dilated cardiomyopathy patients. The marked division of opinion regarding the criterion according to which the optimal angiotensin-converting-enzyme-inhibitor maintenance dose should be established, and the role of aldosterone antagonists are remarkable, since the attitudes discussed in both statements have potential to influence the long-term benefits of therapy.

When evidence is scarce and contradictory, the insights of experts provide a valuable contribution to the decision-making process.[8–10] The output from consensus approaches is rarely an end in itself, dissemination and further use of findings is the ultimate aim of such activities.[10] The external validation of results among specific expert groups may be an interesting next step. Our results might contribute to disseminate paediatric evidence available, especially with regard to angiotensin-converting-enzyme-inhibitors in single ventricle physiology, and serve to promote reducing unjustified variability in everyday practice. We have found areas of common thinking and motivation, which can provide a means of triggering scientific collaboration to cover the named areas of need, both in the form of data sharing in multicentre observational studies or through the creation of large databases to evaluate therapy outcomes and in developing consensus documents that approach specific topics in depth. Rather than producing any changes in clinical practice, the results can be seen as a guide for further research steps and a set of topics upon which scientific projects are more likely to be successfully implemented. The non-consensus statements might serve to give the topics discussed a greater visibility and encourage clinicians to compare outcomes in groups of patients treated according to different strategies, which may help establish the criterion to treat paediatric patients in the most effective way. Until therapeutic recommendations can be made on the basis of solid evidence derived from paediatric randomised controlled trials, we advocate making the best use of available knowledge. We hope this work will help raise awareness that, though not optimal, other research methods can contribute to advancing the goal of safe and effective heart failure pharmacotherapy in children.

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Conflicts of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by Institutional Ethics Committee and Data Protection Officer at the Heinrich-Heine-University Düsseldorf, Germany. This study was conducted in compliance with the European Union Data Protection Directive 95/46/EC. Informed consent was obtained from each participant.

Contributions. S.L. conceived the research idea. C.C. and S.L. contributed to the conception of the study. C.C., N.M., F.K., and H.S. contributed to the study design. Z.B., D.B., H.B., A.H., D.T.H., I.J., F.M., I.M.B., T.P., D.S., A.A.S., S.R., and D.G.W. formed the expert panel. C.C. and N.M. contributed to the experimental part. C.C., F.K., and N.M. contributed to the analysis of data. C.C., F.K., N.M., S.L., M.D., M.M., and I.J. contributed to the interpretation of the study results. C.C., N.M., and S.L. contributed to the elaboration of the study report. C.C. drafted the manuscript. J.W., S.L., H.S., N.M., F.H., M.D., I.J., M.B., and

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References

1. Bajcetic M, Jelisavcic M, Mitrovic J, et al. Off label and unlicensed drugs use in paediatric cardiology. Eur J Clin Pharmacol 2005; 61: 775–779. doi: 10.1007/s00228-005-0981-y
2. 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: 1535–1552. doi: 10.1016/j.cjca.2013.08.008
3. 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
4. EMEA. Evidence of harm from off-label or unlicensed medicines in children. 2004. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004021.pdf
5. Kennedy PJ, Leathley CM, Hughes CF. Clinical practice variation. Med J Aust 2010; 193: S97–S99.
6. Li JS, Colan SD, Sleeper LA, et al. Lessons learned from a pediatric clinical trial: the pediatric heart network angiotensin-converting enzyme inhibition in mitral regurgitation study. Am Heart J 2011; 161: 233–240. doi: 10.1016/j.ahj.2010.10.030
7. Rossano JW, Shaddy RE. Update on pharmacological heart failure therapies in children: do adult medications work in children and if not, why not? Circulation 2014; 129: 607–612. doi: 10.1161/CIRCULATIONAHA.113.003615
8. Fick DM, Cooper JW, Wade WE, et al. Updating the beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003; 163: 2716–2724. doi: 10.1001/archinte.163.22.2716
9. Gurvitz M, Marelli A, Mangione-Smith R, et al. Building quality indicators to improve care for adults with congenital heart disease. J Am Coll Cardiol 2013; 62. doi: 10.1016/j.jacc.2013.07.099
10. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995; 311: 376–380.
11. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000; 32: 1008–1015.
12. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Ärztebl Int 2010; 107: 543–551. doi: 10.3238/arztebl.2010.0543
13. Keeney S, Hasson F, McKenna H. The Delphi technique in nursing and health research. 1st ed. Chichester, United Kingdom: Wiley-Blackwell 2011.
14. Dalkey N. An experimental study of group opinion: the Delphi method. Futures 1969; 1: 408–426. doi: 10.1016/S0016-3287(69)80025-X
15. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014; 67: 401–409. doi: 10.1016/j.jclinepi.2013.12.002
16. Dalkey, Helmer-Hirschberg O. An Experimental Application of the Delphi Method to the Use of Experts. Published Online First: 1962. Retrieved April 19, 2018, from https://www.rand.org/pubs/research_memoranda/RM727z1.html
17. Häder M. Delphi-befragungen: Ein Arbeitsbuch. 3rd ed. Wiesbaden: Springer 2014.
18. Holey EA, Feeley JL, Dixon J, et al. An exploration of the use of simple statistics to measure consensus and stability in Delphi studies. BMC Med Res Methodol 2007; 7: 52. doi: 10.1186/1471-2288-7-52
19. Hsu, Sandford B. The Delphi technique: making sense of consensus. Pract Assess Res Eval 2007; 12: 1–8.
20. Medrano López C, García-Guereta L, Fernández Pineda L, et al. [Clinical consensus on respiratory syncytial virus (RSV) infection prophylaxis and the use of palivizumab in paediatric cardiology.]. An Pediatr Barc Spain 2003 2010; 72: 432.e1–432.e13. doi: 10.1016/j.anpedi.2010.03.001
21. Okoli C, Pawlowski S. The Delphi method as a research tool: an example, design considerations and applications. Inf Manage 2004; 42: 15–29. doi: 10.1016/j.im.2003.11.002
22. Hamzeh NY, Wamboldt FS, Weinberger HD. Management of cardiac sarcoidosis in the United States: a Delphi study. Chest 2012; 141: 154–162. doi: 10.1378/chest.11-0263
23. Hejblum G, Ioos V, Vibert J-F, et al. A web-based Delphi study on the indications of chest radiographs for patients in ICUs. Chest 2008; 133: 1107–1112. doi: 10.1378/chest.06-3014
24. Meijer R, Ihnenfeldt D, Vermeulen M, et al. The use of a modified Delphi procedure for the determination of 26 prognostic factors in the sub-acute stage of stroke. Int J Rehabil Res Int Z Rehabil Rev Int Rech Readaptation 2003; 26: 265–270. doi: 10.1097/01.mrr.0000102660.02099.8f
25. Delbecq A, Ven A, Gustafson D. Group techniques for program planning: A guide to nominal groups and Delphi processes. Gustafson Glenview, III.: Scott, Foresman, 1975.
26. Skulmoski GJ, Hartman F, Krahn J. The Delphi method for graduate research. JITE 2007; 6: 1–21. doi: 10.28945/199
27. United Nations Secretariat, Statistics Division. Standard Country or area codes for statistical use (M49). Stand. Ctry. Area Codes Stat. Use M49. https://unstats.un.org/unsd/methodology/m49 (accessed 20 Apr 2018).
28. Andres L. Designing & Doing Survey Research. 1st ed. London: SAGE 2012.
29. Burns KEA, Duffett M, Kho ME, et al. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ Can Med Assoc J J Assoc Medicale Can 2008; 179: 245–252. doi: 10.1503/cmaj.080372
30. Lozano LM, García-Cueto E, Muñiz J. Effect of the number of response categories on the reliability and validity of rating scales. Methodology 2008; 4: 73–79. doi: 10.1027/1614-2241.4.2.73
31. Schmidt RC. Managing Delphi surveys using nonparametric statistical techniques. Decis Sci 2007; 28: 763–774. doi: 10.1111/j.1540-5915.1997.tb01330.x
32. van der Meulen M, Dalinghaus M, Burch M, et al. Question 1: How safe are ACE inhibitors for heart failure in children? Arch Dis Child 2018; 103: 106–109. doi: 10.1136/archdischild-2017-312774
33. Taketomo C, Hodding J, Kraus D. Pediatric & Neonatal Dosage Handbook. 23rd ed. Hudson, Ohio: Lexi-Comp, Inc 2016.
34. Ross RD. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. Pediatr Cardiol 2012; 33: 1295–1300. doi: 10.1007/s00246-012-0306-8
35. Ross RD. Grading the graders of congestive heart failure in children. J Pediatr 2001; 138: 618–620. doi: 10.1067/mpd.2001.115707
36. Connolly D, Rutkowski M, Auslender M, et al. The New York University pediatric heart failure index: a new method of quantifying chronic heart failure severity in children. J Pediatr 2001; 138: 644–648. doi: 10.1067/mpd.2001.114020
37. 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
38. 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: 409–411. doi: 10.1136/adc.2006.109389
39. 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: 2221–2229. doi: 10.1016/j.clinthera.2012.10.005
40. Gibbons RJ, Gardner TJ, Anderson JL, et al. The American heart association's principles for comparative effectiveness research: a policy statement from the American heart association. Circulation 2009; 119: 2955–2962. doi: 10.1161/CIRCULATIONAHA.109.192518
41. Francke AL, Smit MC, de Veer AJE, et al. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. BMC Med Inform Decis Mak 2008; 8: 38. doi: 10.1186/1472-6947-8-38
42. Zak V, Hsu DT, Pemberton VL, et al. Translating clinical trials into clinical practice: a survey assessing the potential impact of the pediatric heart

https://doi.org/10.1017/S1047951119000660 Published online by Cambridge University Press

network infant single ventricle trial. Cardiol Young 2017; 27: 1265–1270. doi: 10.1017/S104795111600295X
43. Hsu, Zak V, Mahony L, et al. Enalapril in infants with single ventricle: results of a multicenter randomized trial. Circulation 2010; 122: 333–340. doi: 10.1161/CIRCULATIONAHA.109.927988
44. 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.
45. 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: 955–961.
46. 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: 270–275.
47. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200. doi: 10.1093/eurheartj/ehw128
48. 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: 1810–1852. doi: 10.1161/CIR.0b013e31829e8807
49. 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
50. 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: 1454–1470. doi: 10.1016/j.ehj.2004.06.003
51. Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 2006; 296: 1867–1876. doi: 10.1001/jama.296.15.1867
52. Akins RB, Tolson H, Cole BR. Stability of response characteristics of a Delphi panel: application of bootstrap data expansion. BMC Med Res Methodol 2005; 5: 37. doi: 10.1186/1471-2288-5-37
53. Duffield C. The Delphi technique: a comparison of results obtained using two expert panels. Int J Nurs Stud 1993; 30: 227–237.

https://doi.org/10.1017/S1047951119000660 Published online by Cambridge University Press