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Original Article

Translating clinical trials into clinical practice: a survey assessing the potential impact of the Pediatric Heart Network Infant Single Ventricle Trial

Victor Zak,[1] Daphne T. Hsu,[2] Victoria L. Pemberton,[3] Jami C. Levine,[4] Andrew M. Atz,[5] James F. Cnota,[6] Chitra Ravishankar,[7] Piers Barker,[8] Linda M. Lambert,[9] Brian W. McCrindle,[10] Michele A. Frommelt,[11] Karen Altmann,[12] Shan Chen,[1] Richard V. Williams[9] for the Pediatric Heart Network Investigators

[1]*New England Research Institute, Watertown, Massachusetts;* [2]*Children's Hospital at Montefiore/Albert Einstein College of Medicine, New York, New York;* [3]*National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland;* [4]*Boston Children's Hospital, Boston, Massachusetts;* [5]*Medical University of South Carolina, Charleston, South Carolina;* [6]*Cincinnati Children's Hospital, Cincinnati, Ohio;* [7]*The Children's Hospital of Philadelphia, Philadelphia;* [8]*Duke University Medical Center, Durham, North Carolina;* [9]*Primary Children's Medical Center, University of Utah, Salt Lake City, Utah, United States of America;* [10]*The Hospital for Sick Children, University of Toronto, Toronto, Canada;* [11]*Medical College of Wisconsin, Milwaukee, Wisconsin;* [12]*Columbia University Medical Center, New York, New York, United States of America*

Abstract *Background:* A few studies have evaluated the impact of clinical trial results on practice in paediatric cardiology. The Infant Single Ventricle (ISV) Trial results published in 2010 did not support routine use of the angiotensin-converting enzyme inhibitor enalapril in infants with single-ventricle physiology. We sought to assess the influence of these findings on clinical practice. *Methods:* A web-based survey was distributed via e-mail to over 2000 paediatric cardiologists, intensivists, cardiothoracic surgeons, and cardiac advance practice nurses during three distribution periods. The results were analysed using McNemar's test for paired data and Fisher's exact test. *Results:* The response rate was 31.5% (69% cardiologists and 65% with >10 years of experience). Among respondents familiar with trial results, 74% reported current practice consistent with trial findings versus 48% before trial publication ($p < 0.001$); 19% used angiotensin-converting enzyme inhibitor in this population "almost always" versus 36% in the past ($p < 0.001$), and 72% reported a change in management or improved confidence in treatment decisions involving this therapy based on the trial results. Respondents familiar with trial results (78%) were marginally more likely to practise consistent with the trial results than those unfamiliar (74 versus 67%, $p = 0.16$). Among all respondents, 28% reported less frequent use of angiotensin-converting enzyme inhibitor over the last 3 years. *Conclusions:* Within 5 years of publication, the majority of respondents was familiar with the Infant Single Ventricle Trial results and reported less frequent use of angiotensin-converting enzyme inhibitor in single-ventricle infants; however, 28% reported not adjusting their clinical decisions based on the trial's findings.

Keywords: Single-ventricle physiology; angiotensin-converting enzyme inhibitor; physician survey

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DESPITE THE ABSENCE OF EVIDENCE FOR EFFICACY IN infants with single-ventricle physiology, the empirical use of angiotensin-converting enzyme inhibitors to preserve ventricular function, among other potential indications, has been common in the paediatric cardiology community. The National Heart, Lung, and Blood Institute-funded Pediatric Heart Network conducted a randomised, double-blinded, placebo-controlled, multicentre clinical trial comparing the effects of the angiotensin-converting

Correspondence to: V. Zak, PhD, New England Research Institute, 480 Pleasant Street, Watertown, MA 02472, United States of America. Tel: +617 972 3233; Fax: +617 923 4176; E-mail: vzak@neriscience.com

enzyme inhibitor enalapril with placebo in infants with single-ventricle physiology during the first 14 months of life – the Infant Single Ventricle Trial.[1] The results of this clinical trial were published in 2010,[2] and demonstrated no difference in somatic growth, ventricular function, heart failure severity, or neurodevelopmental outcomes between the enalapril-treated and placebo groups. The trial investigators concluded that routine use of angiotensin-converting enzyme inhibitor was not indicated during the 1st year of life in infants with single-ventricle physiology.

The main aims of this survey-based study were to determine how the findings of the Infant Single Ventricle Trial were disseminated to the paediatric cardiology community and what practice changes occurred in the prescription patterns for angiotensin-converting enzyme inhibitor in infants with single-ventricle physiology in the years since publication of the trial results.

Methods

Survey

Instrument. A survey was developed by a subcommittee of Pediatric Heart Network investigators with guidance from outside experts in the field of survey science (see Acknowledgements section). The final survey included 16 multiple-choice questions, with skip-logic as appropriate, designed to assess factors that may influence dissemination and adoption of clinical trial findings into practice (see Appendix in Supplementary material). The survey was designed to allow online completion within 5–10 minutes. No incentive was provided for responding to the survey. All responses were anonymous – that is, the only identifiable information about each user was binary: responded yes/no.

Target sample population. The target sample population included clinical specialists in North America who care for infants and children with CHD, including paediatric cardiologists, cardiac intensivists, cardiothoracic surgeons, and advance practice nurses. A database of e-mail addresses for the target sample group was compiled by the investigators using directories of physicians providing paediatric cardiovascular care and lists available through professional societies and conferences. Specialists classified as paediatric cardiologists in a commercially available database – provided by BtoB Global™ (La Mirada, California, United States of America) – were included in the analyses data sets only if they were certified by the American Board of Pediatrics in Pediatric Cardiology based on an online search.

Distribution. The survey was distributed to the target population via e-mail using SurveyMonkey™, a commercial online survey software tool. The e-mail contained a user-specific link to the survey, the first page of which included the informed consent text for participation. Up to 10 weekly reminder e-mails were sent to non-responders. Potential participants were able to opt out of the survey at any time and receive no further messages. The survey was initially sent to a random sample of 200 e-mail addresses to estimate response rate and evaluate potential responder bias. This was followed by distribution to the remainder of the list during two time periods – either February–April, 2014 or February–April, 2015.

Definitions. Clinical practice "consistent with the key findings of the ISV Trial" was defined as not prescribing angiotensin-converting enzyme inhibitor therapy for the prevention of poor growth, systemic ventricular dysfunction, and/or atrioventricular valve regurgitation. This information was collected for current practice patterns and for practice before publication of the Infant Single Ventricle trial results (questions 5 and 8, respectively, see Appendix in Supplementary material).

Data analysis

Potential bias between respondents and non-respondents was assessed after the pilot distribution by comparing key characteristics such as sex, age/experience, and geographic region that are consistently among the strongest predictors of non-response in surveys between groups, based on the recommendation of the survey science expert. Data for the non-respondents were collected post hoc from internet searches. Changes in practice pattern between two time points – that is, before the trial and after – were assessed using McNemar's test for paired data; differences between subgroups were assessed using Fisher's exact test.

Results

Pilot distribution

Of the 200 randomly selected e-mail addresses for the initial pilot distribution, 174 (87%) were valid. The response rate from this distribution was 49%. There were no significant differences between responders and non-responders in any of the three key factors – sex, years of experience, and geographical location.

Total distribution and response rate

The total distribution list included 2026 valid e-mail addresses, which generated 638 responses (response rate 31.5%). Of these responses, nine did not provide analysable information, including seven non-consent, resulting in 629 responses utilised in further analyses.

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The majority of responses was received within the first 4 weeks after the initial distribution.

Description of respondents

Most respondents identified themselves as paediatric cardiologists (69%), followed by paediatric intensivists (10%), paediatric cardiac surgeons (8%), and advanced practice nurses or nurse practitioners with prescribing privileges (8%). The majority were men (64%), cared for more than 10 infants with single-ventricle physiology per year (60%), and had been in practice for more than 10 years beyond training (65%). Most practised in an academic/university setting (83%), and many (57%) had practised at a PHN site at some point in time.

Influence of the Infant Single Ventricle trial on clinical practice

The majority of respondents were familiar with the results of the trial (78%). Of those, 72% reported that the findings were helpful, with approximately equal split between 35% reporting a change in practice and 37% reporting being more confident in their treatment decisions without changing their practice. The remaining 28% did not find the results helpful for their practice, and did not change their treatment decisions. This group of respondents reported concerns with the Infant Single Ventricle trial design and interpretation of findings (question 10, Appendix) more frequently than the group that reported that the findings of the trial were helpful, including sample size was too small (39 versus 17.5%), end point not relevant (36 versus 9.5%), disagreement with trial design (24 versus 2%), and disagreement with the interpretation of results (14 versus 3%) ($p < 0.001$ for all comparisons above, Fisher's exact test).

Of respondents who were aware of the results and answered questions about both time points (n = 399; Fig 1), 36% almost always used angiotensin-converting enzyme inhibitor before learning the trial results versus 19% after learning the trial results ($p < 0.001$); 56% reported selective use earlier versus 67% after the trial; and 8% never or almost never used this therapy before the trial versus 14% after ($p < 0.001$).

The current practice in 74% of respondents was consistent with the trial's findings as opposed to 48% before learning the trial's findings ($p < 0.001$, Table 1). These changes in clinical practice were reported in all three distributions. At the time of the survey, 28% of respondents reported using angiotensin-converting enzyme inhibitor therapy less frequently in single-ventricle infants <14 months of age compared with the time period before the trial results were published, 9% were using angiotensin-converting enzyme inhibitor therapy more frequently, 18% reported no change, and 45% were not sure.

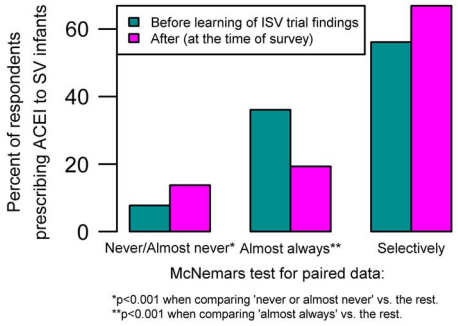

Figure 1.
Change after learning of ISV Trial results in the self-reported frequency of prescribing ACEI to infants with single ventricle physiology <14 months of age. ACEI = angiotensin-converting enzyme inhibitor; ISV = Infant Single Ventricle; SV = single ventricle.

Table 1. Change after learning about the Infant Single Ventricle (ISV) Trial in the proportion of clinicians reporting angiotensin-converting enzyme inhibitor use consistent with trial findings.

		Practice consistent with ISV Trial findings		
Distributions	**n**	**Before (%)**	**After (%)**	**p***
2013	57	47	60	0.09
2014	74	38	74	<0.001
2015	253	52	77	<0.001
Total	384	48	74	<0.001

*McNemar's test for paired data

There was a significant decrease in the reported preventive use of angiotensin-converting enzyme inhibitor among respondents familiar with the Infant Single Ventricle Trial's results (Fig 2a), including for prevention of systemic ventricular dysfunction (50 versus 24%, $p < 0.001$), atrioventricular valve regurgitation (22 versus 13%, $p < 0.001$), hypertension (11 versus 7%, $p = 0.01$), semilunar valve regurgitation (10 versus 7%, $p = 0.02$), and poor growth (9 versus 4%, $p < 0.001$). The use of angiotensin-converting enzyme inhibitor to treat, rather than to prevent, poor growth declined (Fig 2b) from 9 to 6% ($p = 0.05$) and to treat systemic ventricular dysfunction and hypertension increased from 75 to 83% ($p = 0.001$) and 70 to 75% ($p < 0.02$), respectively.

Respondents who had ever practised at a Pediatric Heart Network site were more likely to be familiar with the results of the trial than those who never practised at such a site (89 versus 66%, $p < 0.001$). Although practice patterns of the respondents familiar with the results of the trial were marginally more frequently consistent with trial findings, the difference was not significant (74 versus 67%, $p = 0.16$).

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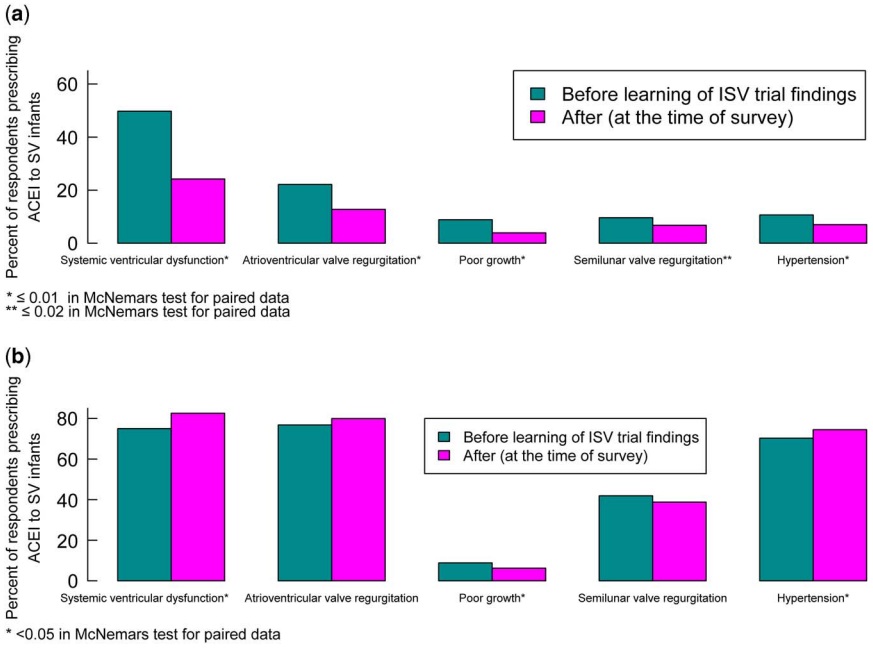

Figure 2.
Change after learning of ISV Trial results in the self-reported proportion of respondents prescribing ACEI to infants with single ventricle physiology to prevent (Fig 2A) or treat (Fig 2B) systemic ventricular dysfunction, atrioventricular valve regurgitation, poor growth, semilunar valve regurgitation, and hypertension. ACEI = angiotensin-converting enzyme inhibitor; ISV = Infant Single Ventricle; SV = single ventricle.

Dissemination and implementation of research results

In general, respondents reported that a publication in a peer-reviewed journal was the most frequent method of gaining knowledge about clinical research findings (94%), followed by presentation at a national meeting (77%), information received from a colleague (74%), and professional website or newsletter (28%). For the Infant Single Ventricle Trial in particular, 69% of respondents reported learning about the trial results from the publication, 37% from a colleague, 24% heard or read about the original presentation at the 2009 American Heart Association Scientific Sessions, and 13% read a brief description elsewhere; 13% of respondents were either actively (6%) or somewhat (7%) involved in the conduct of the trial.

Discussion

This survey of the paediatric cardiology community was conducted to assess the influence of specific clinical trial results on current medical practice. The study revealed a significant change in clinical practice in the care of infants with single-ventricle physiology by 3–5 years following the publication of the Pediatric Heart Network Infant Single Ventricle Trial results.[2] Overall, angiotensin-converting enzyme inhibitor use declined in this population over time, and practitioners familiar with the trial results were less likely to routinely prescribe angiotensin-converting enzyme inhibitor as a preventive therapy compared with before learning the trial results.

There are a few large clinical trials to guide therapy in paediatric cardiology, and often practice is extrapolated from adult trials or guidelines. Angiotensin-converting enzyme inhibitor use in infants and children with single-ventricle physiology is an example of this approach. This class of medications has been shown to have benefits in adults at risk for developing left ventricular systolic dysfunction secondary to acquired heart disease.[3,4] On the basis of these data, many paediatric cardiology practitioners adopted the use of these medications for infants with single-ventricle physiology in the hope that it would prevent clinical deterioration. The rationale for routine angiotensin-converting enzyme inhibitor use was based on the growing body of evidence that children with single-ventricle physiology are at high risk for developing ventricular dysfunction[5] and that these medications are well tolerated.[6] On the other hand, use of a medication that has not been studied in this population carries the risk of exposing patients to unnecessary and potentially unknown side-effects. This survey revealed that before publication of the Infant Single Ventricle Trial results, many of the responders felt that the risk : benefit ratio favoured medication use as a preventive strategy. After the trial results were published, a fewer responders were using angiotensin-converting enzyme inhibitor as a preventive therapy. A small increase in the use of angiotensin-converting enzyme inhibitor to treat

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ventricular dysfunction may be triggered by a decreased preventative use of these medications. Overall, the trial results appear to have shifted the assessment of the risk : benefit ratio in a way that made practitioners less likely to prescribe this therapy in the absence of clinical deterioration.

More than 20% of respondents, however, did not find the Infant Single Ventricle Trial findings helpful and did not change their management decisions on the basis of these results. This group expressed more frequent disagreement with the study design and interpretation of the results. Other factors such as practice inertia and adherence to local, established practice patterns may also have played a role.

Clinical trials are expensive to carry out and are time intensive for both investigators and study participants. The motivation to participate in prospective, placebo-controlled trials is to generate evidence-based data to improve healthcare for patients; thus, it is in the best interest of patients and healthcare providers that trial results impacting patient health and safety be disseminated as efficiently as possible to the practitioners for whom this information is important. There has been little research, however, on how effectively results from paediatric clinical trials are disseminated and, if they are, how long it takes for study recommendations to become incorporated into routine practice.

The incorporation of important research findings into practice may take many years. A number of barriers to implementation of clinical trial results or practice guidelines have been identified and include a lack of awareness or familiarity, lack of agreement with research results, as well as inertia of previous practice and external barriers to implementation.[7] Engagement of physicians utilising multiple strategies – small and large informational meetings and multiple publications of various types – for implementing important research findings and guidelines into practice has proven more effective than single strategies.[8] Interestingly, studies have shown that the timeline for adopting practices shown to be effective in clinical research studies may be shorter than the timeline for abandoning methods that have been shown to be ineffective.[9,10] The routine use of angiotensin-converting enzyme inhibitor therapy in infants with single-ventricle physiology would be an example of the latter, and, therefore, it would be expected that it may take quite some time for practitioners to abandon the use of these medications.

Surprisingly, this survey suggests that the results of the Infant Single Ventricle Trial led to a change in clinical practice over a relatively short period of time. It is interesting to speculate on why this may be true. To some extent, this is likely due to the high profile of the Pediatric Heart Network in the paediatric cardiology community and the relatively small number of prospective multicentre clinical trials carried out in patients with rare heart diseases. Owing to these factors, dissemination of the trial results was fairly extensive. The results were presented in oral abstract form at the 2009 American Heart Association Scientific Sessions and published shortly thereafter in a high-impact journal.[2] The trial results were the subject of two letters to the editor of *Circulation*[11,12] and included in two of the "most read" review articles[13,14] for the years 2010 and 2011. In addition, numerous other studies have been published using the data set generated from this trial, which is now publicly available (http://www.pediatricheartnetwork.org/ForResearchers/PHNPublicUseDatasets/InfantSingleVentricleTrialISV.aspx). Given the large number of cardiologists with ties to the participating centres and the extensive distribution of the results via multiple mechanisms, the relatively rapid incorporation of the results of a negative trial into practice is perhaps not surprising. Although it is gratifying to see that the impact of the trial was fairly rapid, it is also worth highlighting that nearly a quarter of responders were not familiar with the trial. This raises the question of how the field could improve the way that information is disseminated.

It is also interesting to note that the current practice patterns of practitioners not familiar with the results of the trial were not significantly different from those familiar with the trial, suggesting the potential for diffusion of practice patterns across the community. This highlights the fact that there are likely factors other than familiarity with clinical trial results that impact practice decisions. A better understanding of the additional factors that impact practice change may lead to improved dissemination strategies and translation of trial results into practice.

This study has a number of limitations. Results are based on an online survey with a modest response rate. No incentives were offered, which may have negatively impacted the response rate. The list of e-mail contacts was compiled primarily from institutions with paediatric cardiothoracic surgical programmes, skewing the sampled population towards academic practices, which was reflected in the results. There is a possibility that those familiar with the trial were more likely to respond than those not familiar. The results are self-reported practice patterns, which may differ from actual practice. In addition, it is difficult to know whether the reported changes are directly attributable to the Infant Single Ventricle Trial.

In conclusion, the findings of this survey suggest that within 5 years of publication the results of the Pediatric Heart Network Infant Single Ventricle Trial have been incorporated into clinical practice with fewer paediatric cardiology practitioners using angiotensin-converting enzyme inhibitor as a preventive strategy in infants with

single-ventricle physiology. The survey highlighted that the results of this negative study led to a relatively rapid change in practice patterns. Interestingly, this was even true for those who did not have direct knowledge of the trial results; however, over a quarter of respondents familiar with the results of the Infant Single Ventricle Trial reported not adjusting their clinical decisions on the basis of the trial findings for a variety of reasons. The survey also highlighted that dissemination of information from trial results can be improved. Further research on how to improve the dissemination of new information is suggested.

Supplementary materials

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S104795111600295X

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Conflicts of Interest

None.

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