

## Original Article

# Practice Variation Among Canadian Pediatric Cardiologists in Medical Management of Dilated Ascending Aorta in Patients With Bicuspid Aortic Valve

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### ABSTRACT

**Background:** Medical therapy is often prescribed to reduce the rate of aortic dilatation and prevent aortic dissection in patients with bicuspid aortic valve (BAV) despite a lack of evidence. We conducted an anonymous survey to gain insight into Canadian clinical practice regarding medical therapy used to slow the progression of aortic dilatation in patients with BAV.

**Methods:** A questionnaire was sent to 115 paediatric cardiologists and 18 adult congenital heart disease specialists in Canada.

**Results:** Ninety of 113 paediatric cardiologists (80%) completing the questionnaire reported prescribing medication to reduce the rate of aortic dilatation. Some 75% (61/81) of them reported prescribing medications on the basis of aortic size z scores, and 78% (48/61) considered medication at a z score between  $\geq 2$  and  $< 5$ . The remaining 25% of responders (20/81) reported prescribing medications on the basis of absolute aortic diameter, and 80% (16/20) of them considered initiating medical therapy at an aortic diameter  $> 40$  mm to  $< 50$  mm. For practical purposes, however, 40% of respondents (45/113) would not or rarely consider medical therapy for this indication because of variation in the threshold for initiating

### RÉSUMÉ

**Introduction :** En dépit du manque de données probantes, un traitement médical est souvent prescrit pour réduire le taux de dilatation aortique et prévenir la dissection aortique chez les patients ayant une bicuspidie aortique (BA). Nous avons mené une enquête anonyme pour avoir un aperçu de la pratique clinique au Canada en ce qui concerne le traitement médical utilisé pour ralentir la progression de la dilatation aortique chez les patients ayant une BA.

**Méthodes :** Nous avons envoyé un questionnaire à 115 cardiologues en pédiatrie et à 18 spécialistes en cardiopathie congénitale de l'adulte du Canada.

**Résultats :** Quatre-vingt-dix des 113 cardiologues en pédiatrie (80 %) ayant rempli le questionnaire ont signalé prescrire des médicaments pour réduire le taux de dilatation aortique. Certains d'entre eux, soit 75 % (61/81) ont signalé prescrire des médicaments en fonction du Z-score de la taille aortique, et 78 % (48/61) ont envisagé de prescrire les médicaments lorsque le Z-score était entre  $\geq 2$  et  $< 5$ . Les 25 % de répondants restants (20/81) ont signalé prescrire des médicaments en fonction du diamètre aortique absolu, et 80 % (16/20) d'entre eux ont envisagé de faire commencer le traitement médical lorsque le

Bicuspid aortic valve (BAV) is the most common congenital heart disease, affecting 1% to 2% of the population. Approximately 40% to 50% of these children are estimated to develop aortopathy, causing dilatation of the ascending aorta,<sup>1,2</sup> ultimately resulting in the formation of an aortic aneurysm and a risk of aortic dissection during young adulthood.<sup>3–5</sup> However, the rate of aortic dilation in children appears to be variable, with

other authors reporting minimal changes in the ascending aortas of young children over a 9-year follow-up period.<sup>1,6</sup> The incidence of aortic dissection is low, occurring in 0.03% to 0.1% of all patients with BAV, but increases to approximately 0.4% to 0.5% of patients with BAV at  $> 50$  years of age.<sup>4,5</sup> The lifetime risk of aortic dissection is estimated to be 6.1%, which is approximately 8 to 9 times higher than that of the general population.<sup>4,5</sup> On the basis of current guidelines, 5% to 9% of adult patients with BAV are estimated to require prophylactic aneurysm surgery over a 20-year period.<sup>4</sup> Therefore, slowing the progression of aortic dilatation would be a logical therapeutic target.

Despite the lack of concrete evidence for or against medical treatment of aortopathy in patients with BAV, many still receive medications to potentially reduce aortic wall stress and thus slow the rate of dilatation according to the law of Laplace.<sup>7</sup> Medications, such as beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor

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See page 122 for disclosure information.

treatment. Ten of 14 adult congenital heart disease specialists' responses (71%), reported prescribing medications who were excluded because of missing data.

**Conclusion:** The majority of Canadian paediatric cardiologists reported prescribing medications to slow the rate of aortic dilatation in patients with BAV. However, there is heterogeneity in the criteria to prescribe medical therapy. A multicenter randomized controlled trial is needed to establish the role of medical therapy in this patient population.

blockers (ARBs) that theoretically reduce aortic wall stress by reducing blood pressure seem to slow the progression of aortopathy in Marfan's syndrome and are often prescribed to patients with BAV associated aortopathy.<sup>8</sup> ARBs may have an additional favourable effect on maintaining the integrity of the aortic wall connective tissue,<sup>7</sup> but clinical studies have not shown significant advantage over beta-blockers.<sup>8</sup>

There are no published standardized criteria to select patients for medical therapy or to select which therapy would be most beneficial. Furthermore, the data to support decision-making in paediatric patients are extremely limited.

To characterize the spectrum of practice of paediatric cardiologists and adult congenital heart disease (ACHD) specialists in Canada regarding medical treatment of dilated aorta in BAV patients, we conducted a questionnaire-based study.

## Methods

A questionnaire (Table 1) consisting of 9 questions (Q1-Q9) was developed to ask Canadian paediatric cardiologists and ACHD specialists about their practice of prescribing medical treatment to patients with BAV and aortic dilatation for the purpose of slowing the rate of aortic dilatation. Two of the study investigators drafted the initial questionnaire. The remaining 2 investigators and 2 other paediatric cardiologists reviewed and subsequently revised it to optimize brevity and clarity. The Institutional Research Ethics Board approved this study. The names and email addresses of potential participants were obtained from the official website of the Canadian Pediatric Cardiology Association and Canadian Adult Congenital Heart Network ([www.cachnet.org](http://www.cachnet.org)), which maintain records of almost all paediatric cardiologists and adult congenital cardiac specialists at each academic centre in Canada, regardless of membership status.

Electronic invitations were sent to 96 paediatric cardiologists and 18 adult congenital heart specialists. Two reminders were sent at 3-week intervals. To improve participation rates, hard copies of the questionnaire were distributed to 19 paediatric cardiologists at the annual Canadian Cardiovascular Congress meeting. Participants invited via email were encouraged to forward the link to their colleagues, if they were not already invited. To avoid duplicate responses, a request to only complete the questionnaire once was placed at the top of the survey. All responses were anonymous and could not be traced to the practitioner completing the survey.

diamètre aortique était entre  $> 40$  mm et  $< 50$  mm. Concrètement, toutefois, 40 % des répondants (45/113) n'ont pas envisagé ou ont rarement envisagé de prescrire un traitement médical pour cette indication en raison de la variation dans le seuil de mise en place du traitement. Dix des 14 réponses (71 %) des spécialistes de la cardiopathie congénitale de l'adulte ont signalé prescrire des médicaments qui étaient exclus en raison de données manquantes.

**Conclusion :** La majorité des cardiologues en pédiatrie du Canada ont signalé prescrire des médicaments pour ralentir le taux de dilatation aortique chez les patients ayant une BA. Toutefois, les critères utilisés pour prescrire un traitement médical sont hétérogènes. Un essai clinique multicentrique et à répartition aléatoire est nécessaire pour déterminer le rôle du traitement médical dans cette population de patients.

## Results

A total of 113 responses were received from the participants: 18 hard copies and 95 electronic responses, giving a response rate of 98% (assuming that no one distributed the questionnaire to other colleagues or completed it twice). Only 14 ACHD specialists' responses were received and 10 of 14

**Table 1. Summary of all the responses to questionnaire (n = 113)**

Questionnaire "Aortic Dilatation in Association With Bicuspid Aortic Valve" Note: Please do not fill this questionnaire, if you have already completed it once	
Questions:	Cardiologist No. (%)
1. Do you use medications to reduce the rate of aortic dilation?	Yes: 90/113 (80%) No: 23/113 (20%)
2. What criteria do you use to assess severity of ascending aorta dilatation?	z value: 61/81 (75 %) Absolute aortic diameter: 20/81 (25 %)
3. At what z value of ascending aorta (at any level) do you start medical therapy to slow progression of dilatation? (n = 61)	$\geq 2 = 16$ (26%), $\geq 3 = 23$ (38 %) $\geq 4 = 9$ (15%), $\geq 5 = 5$ (8%) $\geq 6 = 5$ (8%), Other = 3 (5%)
4. If you use absolute dimension (mm), at what aortic diameter do you initiate medical therapy? (n = 20)	$> 35 = 3$ (15%), $> 40 = 13$ (65%) $> 45 = 3$ (15%), $> 50 = 1$ (5%)
5. What medication is your first choice?	$\beta$ -Blockers: 49 (61 %) ARB: 24 (30 %) ACEI: 7 (9%) Missing: 1
6. Do you add a medication from second group if aortic dilatation continues to progress despite using 1 medication?	Yes: 45 (56 %) No: 36 (44 %)
7. Do any 1 or more of the following factors influence your decision to initiate medical therapy?	Family history of aortic aneurysm/dissection = 73 (90 %) Hypertension = 49 (61%) Other (not specified) = 10 (12%)
8. How would you describe your practice?	Academic = 55 (68%) Community = 10 (12%) Both = 16 (20%)
9. I am a	Pediatric cardiologist = 113 ACHD specialist = 14

ACEI, angiotensin-converting enzyme inhibitor; ACHD, adult congenital heart disease; ARB, angiotensin receptor blocker.

(71%) of them reported prescribing medication to reduce the rate of aortic dilatation. Further analysis was not performed for inadequate data quality because of incomplete responses.

Eighty percent (90/113) of respondents reported prescribing medications for patients with BAV at some point to reduce the rate of dilation. Of those 90 individuals prescribing medications, 9 did not provide the criteria used to initiate medical therapy and are excluded from the analysis. The responses of the remaining 81 completed surveys are summarized in Table 1. The majority of practitioners, 61 of 81 (75%), reported prescribing medications on the basis of aortic size  $z$  scores. A large proportion, 78% (48/61), of respondents reported prescribing medication at a  $z$  score from “ $\geq 2$  to  $< 5$ .” The remaining 20 (25%) of 81 complete responders reported prescribing medications on the basis of absolute aortic diameter and 80% (16/20) of that group reported considering medical therapy at an aortic diameter “ $> 40$  mm to  $< 50$  mm.” Beta-blockers were reported as the most commonly prescribed medication (61%), but a minority (30%) reported prescribing ARBs and a small number of practitioners reported prescribing angiotensin-converting enzyme inhibitors. Approximately half of all responders reported considering dual medical therapy if aortic dilatation continues to progress on single-agent therapy. Most of the practitioners reported a family history of aortic aneurysm, aortic dissection, and hypertension (defined as systolic or diastolic blood pressure  $\geq 95$ th percentile for gender, age, and height on 3 repeated measurements)<sup>9</sup> as an important consideration in favour of initiating medical treatment (Table 1). No practitioners reported using rate of change of aortic size or  $z$ -score as an additional factor in decision-making about therapy initiation or type of agent used.

## Discussion

The results of this survey demonstrate that approximately 80% of Canadian paediatric cardiologists reported prescribing medications to slow aortic dilatation in patients with BAV. However, we noted a wide variation among practitioners regarding the threshold for, as well as choice of, a pharmacologic agent. Forty-eight respondents preferred early intervention, prescribing medical therapy for aortic  $z$  score  $\geq 2$  and  $< 5$ , which correspond to mild and moderate aortic dilatation, respectively (Table 1). In contrast, 27% of respondents (22/81) considered only severe aortic dilation ( $z$  score  $> 6$  or absolute ascending aorta dimensions  $> 40$  mm) as an indication to start medical therapy (Table 1), which is rarely seen in children aged  $< 18$  years with BAV.<sup>1</sup> These paediatric cardiologists represent a more conservative group of practitioners. In addition, 20% of paediatric cardiologists (23/113) reported not prescribing any medical treatment at all to these patients. Thus, 40% (45/113) (Table 1) of the responding paediatric cardiologists would either not or rarely consider medical treatment for this indication.

Similar heterogeneity seems to exist regarding the choice of therapeutic agent prescribed. Moreover, approximately half of the responders reported considering dual medical therapy if aortic dilatation continues to progress on single therapy.

Aortic dilatation begins to manifest and progresses during childhood,<sup>1</sup> and approximately 50% of the adults are

affected by the third decade. Moderate dilatation of ascending aorta, defined as  $z$  value  $\geq 4$ , may occur in approximately 15% of children,<sup>1</sup> and  $> 25\%$  of adults are estimated to develop aneurysmal dilation of ascending aorta, defined as diameter  $\geq 45$  mm within 25 years of diagnosis.<sup>4</sup> Patients with aortic aneurysm are at risk of developing aortic dissection, the risk of which increases with age.<sup>4</sup> Despite surgical advancements, the associated mortality with dissection continues to remain high at close to 25%.<sup>10–12</sup> Thus, it is not surprising that Canadian paediatric cardiologists seek to prevent this complication through initiation of treatment. In a relatively small, retrospective study, Warren et al.<sup>2</sup> observed a possible protective role of beta-blockers against aortic dilatation in children with BAV associated aortopathy. Besides this study, no other prospective or retrospective study examining the role of medical therapy in this population has been published to date. Therefore, there is no consensus regarding medical therapy to slow aortic dilatation in BAV-related aortopathy. Still, many of these patients receive medical therapy based on extrapolation of evidence from patients with aortopathy associated with Marfan or Loeys–Dietz syndrome.<sup>13–15</sup> The American Heart Association guidelines in 2010 suggested prescribing blood pressure–lowering medications to slow progression of aortic dilatation in normotensive adult patients only if they had developed aortic aneurysm.<sup>16</sup> In contrast, more recent North American practice guidelines do not recommend any medical therapy other than treating hypertension.<sup>17,18</sup> The results of the current survey suggest that although many paediatric cardiologists comply with the recommendation of not routinely prescribing medical therapy, a majority of them report prescribing medications to slow the progression of aortic dilatation in children with a variable degree of BAV-associated aortopathy, including mild aortic dilatation.

In our study, some practitioners reported using absolute numbers to guide initiation of therapy. However, given that paediatric patients are growing, there is a need for values normalized to patient size. The most common method of doing this is to use  $z$  scores based on body surface area. Most practitioners used a  $z$  score value of between  $+2$  and  $+5$  for initiation of therapy. This is a wide range and likely reflects the uncertainty around therapeutic decision-making within the community.

To answer the question of whether treatment of patients with BAV and aortic dilation offers therapeutic benefit, and if so, when, and with what agent, further research will be required. A prospective randomized clinical trial titled “Beta Blockers and Angiotensin Receptor Blockers in Bicuspid Aortic Valve Disease Aortopathy (BAV)” (Clinicaltrial.gov NCT01202721) targeting the adult population with BAV has recently completed patient recruitment. No data have yet been released. However, we would speculate that the magnitude of the beneficial effect of medical therapy might be limited, given the advanced degree of aortopathy and aortic dilatation in the adult population as suggested by the law of Laplace.<sup>10</sup> Nonetheless, clarification of whether it is true in paediatric patients is urgently needed. All medications have side effects, and practitioners do not want to subject patients to unnecessary treatment, even when such treatment can reasonably be construed as “largely benign.”

## Study limitations

A warning was posted for participants at the very top of the survey to not respond more than once. However, we cannot rule out the occurrence of duplicate electronic responses from participants who may have already completed the hard copy or vice versa. Participants were asked to forward the survey link to their colleagues. This might have occurred, and in such a case, the denominator may be different than reported. This may also be the explanation for the unusually high survey response rate. We think that such occurrences would be rare, and therefore not meaningfully alter the overall results of the survey. Practices around the threshold and type of medication used were self-reported by respondents and, as such, are subject to recall bias. Therefore, the study results may or may not reflect actual clinical practice for individuals. Participants were not asked in the questionnaire about details of “other factors” influencing their decision to prescribe medication and about the choice of second medication when considering dual therapy. This could have provided further information about their practices, but we opted against it to keep the questionnaire concise.

Some practitioners, such as those primarily devoted to subspecialty practice of critical care or interventional cardiology, who completed the survey may not have much exposure to this patient population, which might have influenced their responses. The questionnaire did not inquire of the participants if they considered a specific threshold of annual rate of progression of aortic dilatation in deciding on therapeutic intervention. In light of recommendations to consider rapid dilation an additional indication to start therapy, this would have been a useful question. The survey was conducted in English, so it may not represent the practitioners who are practicing in French, Canada's other official language.

## Conclusion

There is marked heterogeneity in the current clinical practice of Canadian paediatric cardiologists regarding prescription of medical treatment to reduce the rate of aortic dilatation in children with BAV-associated aortopathy. Two markedly different approaches exist because approximately half of practitioners either do not or rarely prescribe any medical treatment for this group of patients, and an equally large group prefers prescribing medications at an early stage of the aortopathy. Further practice variations exist with regard to the threshold for initiating medical therapy and choice of therapeutic agent. Because more than 80% of practicing Canadian paediatric cardiologists completed the survey, we are comfortable concluding that the results are representative of clinical practice in Canada.

There is a need to standardize the approach to the medical intervention for this patient population with the most common congenital heart disease. A multicenter, prospective, randomized, controlled trial could be helpful in establishing the role of such medical therapy in children and adolescents with BAV aortopathy.

## Disclosures

The authors have no conflicts of interest to disclose.

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