

openheart Predictors of β -blocker adherence in cardiac inherited disease

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ABSTRACT

Objective The cardiac inherited disease (CID) population has suboptimal adherence to long-term β -blocker therapy, which is known to be a risk for sudden cardiac death. This study aimed to identify the clinical and psychosocial variables associated with non-adherence in this population.

Methods 130 individuals (aged 16–81 years, median: 54) from the New Zealand Cardiac Inherited Disease Registry taking β -blockers participated: 65 (50%) long QT syndrome, 42 (32%) hypertrophic cardiomyopathy and 23 (18%) other. Participants completed one questionnaire recording self-reported adherence, anxiety, depression, confidence in taking medication, illness perceptions and medication beliefs. Demographic and clinical variables were taken from the registry.

Results 21 participants (16%) were classed as non-adherent. Bivariate analysis showed that self-reported adherence was worse in those who were younger ($p < 0.001$), had a channelopathy not cardiomyopathy ($p < 0.01$), reported lower confidence in taking β -blockers ($p < 0.001$), had high concerns ($p < 0.05$) and low necessity beliefs about their β -blocker ($p < 0.001$), a poorer understanding of their CID ($p < 0.01$), and lower treatment control beliefs ($p < 0.01$). These variables accounted for 37% of the variance in adherence in a linear regression model. Stronger beliefs around medication necessity and higher confidence in their ability to take their medication predicted β -blocker adherence.

Conclusions Factors associated with β -blocker non-adherence in patients with CID include young age, having a channelopathy, negative medication beliefs, low confidence in taking medication and poor illness perceptions. These findings present an opportunity to develop targeted interventions to improve adherence.

INTRODUCTION

β -blockers prevent symptoms and sudden death in the cardiac ion channelopathies long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT), and are essential adjuvant therapy in various cardiomyopathies.^{1–2} Non-adherence rates among cardiac patients in general are estimated to be around 40%.³ Non-adherence costs the individual through suboptimal treatment benefits, contributes to reduced daily functioning and quality of life, and increases

Key questions

What is already known about this subject?

- ▶ Existing research has identified that a significant proportion of patients with a cardiac inherited disease are not adhering to their β -blocker regimen, a factor known to leave them exposed to risk of symptoms including sudden cardiac death.
- ▶ Variables associated with non-adherence are unknown in this population.

What does this study add?

- ▶ Six variables associated with non-adherence were identified, and these included younger age and having a channelopathy as opposed to a cardiomyopathy.
- ▶ Patients' confidence in their own ability to take the medication each day was important, as was a poorer perceived understanding of their condition.
- ▶ Also contributing was their belief around how necessary the β -blockers are, along with lower confidence in the efficacy of β -blockers in controlling their condition.

How might this impact on clinical practice?

- ▶ These findings are a first step in helping clinicians to identify those patients with cardiac inherited disease who will be non-adherent, thereby highlighting patient groups and variables that could be targeted for intervention.

mortality risk.⁴ There are societal costs associated with non-adherence as well, including increased risk of hospitalisation.⁵

Despite the unique characteristics of the cardiac inherited disease (CID) population, including relative youth, the familial nature of the condition and the pervasive risk of sudden cardiac death, only three studies to date have investigated adherence specifically in patients with a CID. One retrospective registry-based study of long QT syndrome suggested that non-adherence is responsible for almost all patients who suffer a cardiac arrest/sudden death.⁶ Adherence rates to β -blockers in a long QT syndrome study using electronic pharmacy records in the greater Auckland region of New Zealand found that 51% of patients did not have enough



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pills for optimal adherence, including 10% who had not even collected their first prescription.⁷ This implies that only half of this patient population is continuously protected from potentially life-threatening symptoms. Possible risk factors for non-adherence, including age, sex, clinical presentation, family history of sudden death, ethnicity and deprivation index, did not predict non-adherence in this study. The third study looked at adherence in patients with hypertrophic cardiomyopathy and found 30% suboptimal adherence, and the factors associated with poor adherence were younger age, minority ethnicity, anxiety and poor 'mental quality of life'.⁸

Five categories have been identified as influencing adherence to prescribed medical therapy in general (including medication, diet, exercise and lifestyle changes): patient-centred factors (eg, beliefs about medication); therapy-related factors (eg, side effects); health-care system factors (eg, long waiting times); social and economic factors (eg, cost of medication); and disease factors (eg, symptoms).⁹ Within patient-centred factors, a significant body of research has investigated psychosocial variables and their relationship with non-adherence, including beliefs about medication, perceptions about illness, confidence in taking medication (self-efficacy) and mental health.

The current study aims to progress our understanding of the predictors of non-adherence among patients with CID.

METHODS

Study design and study population

Eligible participants were identified on the New Zealand Cardiac Inherited Diseases Registry¹⁰ in May 2017. They had a 'definitely affected' or 'probably affected' clinical status and a genetic status of 'positive', 'uninformative testing' or 'unclassified variant'. Further inclusion criteria included proficiency in English and aged 16 years or older.

An invitation to participate was sent to 618 individuals via email or post in May 2017 and an advertisement was put on the New Zealand CID Group Facebook page. Participants were given 3 months to complete and return the questionnaires to the researchers. The invitation included a participant information sheet, consent form and a questionnaire. A total of 202 individuals gave informed consent and returned the questionnaire (34% response rate), and of these 131 reported they had been prescribed β -blockers. One individual did not complete the last page of the questionnaire and was unidentifiable, so was not included in the final sample of 130. The questionnaire measured a number of psychological and clinical constructs, as listed below.

Predictor variables

The medication-specific subscale of the Beliefs about Medicines Questionnaire (BMQ)¹¹ is commonly used in adherence research. It consists of five statements about

perceived necessity for a medication, for example 'My health in the future will depend on my beta-blocker', and five statements about concerns about the medication, for example 'Having to take a beta-blocker worries me'. Participants are asked to rate how much they agree or disagree with each statement on a 5-point Likert scale. The validation study included patients with a variety of different health conditions, including a general cardiac population, and found satisfactory internal consistency and test-retest reliability.¹¹

The Medication Adherence Self-Efficacy Scale-Revised (MASES-R)¹² was designed to measure an individual's confidence in taking their medication across 13 different situations, such as 'There is no one to remind you' or 'You do not have any symptoms'. Participants respond on a 4-point scale from 'Not at all confident' to 'Extremely confident', with higher scores indicating more confidence. This measure has good internal consistency, test-retest reliability, as well as concurrent and predictive validity.¹²

The Brief Illness Perception Questionnaire (BIPQ)¹³ was used to assess participants' cognitive and emotional representations of their illness. This measure assesses people's lay understanding of their illness, including their ideas about the cause, timeline and controllability of the condition, how much they think they understand it, and the impact it has on their life. Example items include 'How much do you think your treatment can help control your heart condition?' (treatment control) and 'how well do you feel you understand your heart condition?' (coherence). The scale has nine items in total, eight of which have a 10-point rating scale, and the final item asks patients to list what they believe are the top 3 causes of their condition. The questionnaire has been used with a wide variety of illness groups¹³ and has good test-retest reliability, and strong concurrent and predictive validity.

Depression and anxiety were measured using the Patient Health Questionnaire-9 (PHQ-9)¹⁴ and the Generalised Anxiety Disorder-7 (GAD-7),¹⁵ respectively. Both measures ask individuals to report how often they experienced symptoms of depression/anxiety in the last 2 weeks. An example symptom from the PHQ-9 is 'little interest or pleasure in doing things'. An example from the GAD-7 is 'feeling nervous, anxious or on edge'. Responses were recorded on a 4-point scale and ranged from 'Not at all' to 'Nearly every day'. Criterion validity for depression and anxiety has been established against structured mental health professional interviews. A cut-off score of ≥ 10 on the PHQ-9 had a sensitivity of 88% and a specificity of 88% for major depression. A cut-off score of ≥ 10 on the GAD-7 had a sensitivity of 89% and a specificity of 82% for a diagnosis of clinical levels of anxiety.

The service administrator extracted patients' clinical information from the registry, including their diagnosis, clinical, genetic and proband status, time since diagnosis, and CID deaths in the family.

Outcome variables

Adherence was recorded using two standardised self-report measures, the Medication Adherence Report Scale-5 (MARS-5) and the Brief Adherence Rating Scale (BARS), which were significantly related ($r_s=0.63$, $p<0.001$). The MARS-5 has five adherence statements, for example 'I forget to take my β -blocker', and participants are asked to rate how much each statement applies to them. Responses are given on a 5-point scale from 'Always' to 'Never'. This measure has been used in other cardiac populations.¹⁶

The BARS¹⁷ is a scale that is typically used in psychiatric populations. It has four items which measure understanding of regimen and adherence. Item 4 is an adherence variable; it asks people what proportion of their medication they have taken in the last 4 weeks, and participants respond on a visual analogue rating scale from 0% to 100%. Scores below 80% are considered non-adherent, and this cut-off level is typical of other adherence research, including Waddell-Smith and colleagues.⁷ The BARS validation study showed it had good internal consistency, test-retest reliability and good concurrent validity. The BARS had good sensitivity (73%) and specificity (74%) identifying individuals who were non-adherent based on electronic monitoring. The BARS is usually administered by physicians during consultations; however, in this study patients completed the BARS themselves.

Statistical analysis

The data were analysed using SPSS V.24 software. The data were not normally distributed, so non-parametric tests were used for analysis and medians used when reporting results.

Missing data were left out of analysis on a case-by-case basis. One participant had missing data for ethnicity, one for adherence, one for gender and two for genetic results. There were also missing data for death within the family for four participants. There were 126–128 cases included in the preliminary analyses (Spearman's correlations, Mann-Whitney and Kruskal-Wallis tests) and 121 cases in the regression analysis. Spearman's correlations were conducted to investigate associations between psychological variables, age and adherence. Mann-Whitney and Kruskal-Wallis tests were applied to categorical data to assess whether there were any differences in adherence based on proband, clinical and genetic status, and whether there had been death in the family. Multiple linear regression analysis was then performed including variables that were associated with adherence on a bivariate level. An α level of 0.05 was maintained for statistical significance.

Analysis was conducted with the BARS and MARS separately, and the results were very similar across both measures; however, the BARS and MARS assess slightly different aspects of adherence, so a combined score was therefore considered a more comprehensive measure of adherence overall. A combination score was created by converting individual scores to z-scores for the BARS and

MARS and then averaging them. This combination score was used in the correlation and regression analyses.

RESULTS

There were no significant differences between participants and non-participants based on clinical variables. However, there were significant differences in age and ethnicity; those who participated were significantly older (median 53 years, IQR 37–63, vs 45 years, IQR 29–57; $p<0.001$) and they were more likely to be New Zealand European ($p<0.001$). Table 1 presents the demographic and clinical variables of the 130 individuals who participated in the research and reported they had been prescribed β -blockers.

The rate of adherence using item 4 from the BARS found that adherence ranged from 0% to 100% with a median of 98%. Twenty-one (16%) participants reported an adherence rate of less than 80%, and seven (5%) of those participants disclosed they had been prescribed β -blockers, but were not taking them at all. Scores on the MARS-5 scale ranged from 5 to 25, with a median score of 24, and 36% of the participants reported a score of 25 (perfect adherence).

Gender, ethnicity, clinical, genetic or proband status, time since diagnosis, and CID deaths in the family were not significantly associated with adherence. However, older age was significantly associated with higher adherence ($r_s=0.34$, $p<0.001$). In addition, participants with channelopathy had significantly poorer adherence than participants with cardiomyopathy ($U=1476$, $z=-2.61$, $p<0.01$, $d=0.47$).

Beliefs about medication, two domains of illness perceptions and confidence in taking β -blockers were all found to be significantly associated with adherence, as displayed in table 2. Based on these results, age, channelopathy versus cardiomyopathy, MASES-R, BMQ-necessity, BMQ-concern, BIPQ-treatment control and BIPQ-coherence (how much a patient thinks they understand their condition) were entered into linear regression analysis to predict adherence (table 3).

Age and channelopathy versus cardiomyopathy were entered at step 1, which explained 10.7% of the variance in adherence. Step 2 included BIPQ-treatment control, BIPQ-coherence, BMQ-necessity, BMQ-concern and MASES-R, and the total variance explained by the model as a whole was 37.3% (adjusted $r^2=33.5\%$), $F(7, 113)=9.62$, $p<0.001$. Step 2 explained an additional 26.6% of the variance in self-reported adherence, F change (5, 113)=9.60, $p<0.001$. In the final model, having higher medication necessity beliefs and higher reported levels of confidence with taking β -blockers were unique predictors of better adherence.

DISCUSSION

Regular β -blocker medication is the cornerstone of therapy for long QT syndrome and CPVT; however, adherence is known to be poor and yet there has been

Table 1 Demographic and clinical variables of patients with cardiac inherited disease taking part in the study

	Participants (N=130) n (%)
Demographic characteristics	
Age: range (median)	16–81 (54)
Sex: female	74 (57)
Ethnicity	
New Zealand European	101 (77)
Māori and Pacific	17 (13)
Other	11 (9)
Clinical characteristics	
Inherited cardiac condition	
Long QT syndrome	65 (50)
Hypertrophic cardiomyopathy	42 (32)
Dilated cardiomyopathy	10 (8)
Brugada	3 (2)
Other	10 (8)
ARVC	4 (3)
CPVT	5 (4)
Sudden cardiac arrest syndrome	1 (1)
Clinical status	
Definitely affected	104 (80)
Probably affected	26 (20)
Genetic status	
Positive	78 (60)
Testing uninformative	37 (28)
Unclassified variant	13 (10)
Proband	
True	88 (68)
False	42 (32)
Deaths within the family	
Yes	52 (40)
No	51 (39)
I don't know	23 (18)
Number of years since diagnosis, range (median)	0–51 (10)

CPVT, catecholaminergic polymorphic ventricular tachycardia.
ARVC, Arrhythmogenic Right Ventricular Cardiomyopathy.

little research aimed at addressing the problem. Unsurprisingly, this study finds that key indicators for non-adherence are in areas which are not familiar territory for the cardiologist. Yet it is imperative, if patients with CID are to be protected from sudden death, that clinicians in this area develop some understanding of the issues.

The variables associated with non-adherence in this study were younger age, having a channelopathy, lower confidence in ability to take medication appropriately, weaker beliefs about the necessity of the β -blocker

along with greater concern about taking them, and lower perceptions of treatment control and illness coherence. Rather than any particular disease feature, it was simply self-confidence in their own ability to take β -blockers and their belief as to how essential the medication was which were the strongest predictors of adherence. These findings are consistent with previous research across different health conditions, ages and cultures,^{18–21} and present a significant opportunity to intervene and improve adherence. For a start, a simple question enquiring about the patient's own beliefs as to their ability to adhere to therapy will help to find patients who need additional support with their medication regimen.

A model known as the necessity-concerns framework states that people are continually weighing up whether they will take their medication, by balancing concerns about taking the medication with their beliefs of its necessity. Necessity beliefs were found to be of particular importance in this study and so could be targeted for modification in intervention studies.²² Another model known as the Common Sense Model of Illness²³ states that individuals actively try to make sense of their illness by developing cognitive representations of the illness (illness perceptions) which cover different domains, including the identity of the condition (how much a person experiences symptoms they associate with the condition), the consequences it has on their life, what has caused the condition, how long it will last for, and whether the condition is controllable (personally or through treatment). The model proposes that illness perceptions drive how a patient copes with the condition, which includes whether they take their medication or not. The association between illness perceptions and adherence has been found in other cardiac studies.²⁴ Unsurprisingly, we found patients with CID were less likely to take their medication if they believed β -blockers were less effective in controlling their CID. In addition, poor patient understanding about their heart condition was related to poor adherence. The genetic and clinical aspects of CIDs are very complex for lay people and patients to understand. So the onus is on clinicians to ensure patients leave consultations with a good understanding of their condition, as a patient who does not understand is likely to be poorly motivated to adhere to any recommendations made in that consultation. Two clinical/demographic factors were associated with adherence: older age and having a cardiomyopathy rather than a channelopathy. Given non-participants were significantly younger than participants, and younger age was associated with poorer adherence, it is likely the rate of non-adherence in this study is underestimated. However, age has been found to be an inconsistent variable in relation to adherence in general and with CID populations.^{7–9} It may be that the relationship between age and adherence is a non-linear one. There are differences between channelopathies and cardiomyopathies that could

Table 2 Psychological variables significantly associated with the combined adherence z-scores and with the BARS scores which were dichotomised to show adherence ($\geq 80\%$) and non-adherence ($\leq 80\%$) among patients with cardiac inherited disease

Spearman's r correlations	Combined z-score		BARS		
	r_s	P values	Non-adherent Median	Adherent Median	P values
MASES-R	0.574	<0.001	2.5	3.81	<0.001
BMQ-necessity	0.345	<0.001	13.5	18	<0.001
BMQ-concern	-0.210	<0.05	12.5	11	0.381
BIPQ-treatment control	0.293	<0.01	5.5	8	<0.001
BIPQ-coherence	0.232	<0.01	5.5	8	<0.05

BARS, Brief Adherence Rating Scale; BIPQ, Brief Illness Perception Questionnaire; BMQ, Beliefs about Medicines Questionnaire; MASES-R, Medication Adherence Self-Efficacy Scale-Revised.

intuitively explain differences in adherence rates. The heart's ability to function normally tends to deteriorate with age in cardiomyopathies, which is not typically the case with channelopathies. Symptomatic deterioration with cardiomyopathies could provide a reminder that the medication is necessary. Indeed, patients with cardiomyopathy reported more symptoms (both related and unrelated to the disease) than patients with channelopathy, and patients with cardiomyopathy held significantly stronger beliefs around the necessity of β -blockers than patients with channelopathy did. Symptoms have been identified as an important factor for adherence in other research.⁹ However, the reason patients with channelopathy reported poorer adherence is likely to be complex and multifactorial. In the current study neither symptom experience nor disease severity was related to adherence directly; however, they were related to beliefs about medication necessity.

Given this was a cross-sectional study, providing only a single time point, a longitudinal study would help to establish how these variables relate to each other over time.

Implications

Interventions to improve adherence in patients with CID will have the greatest impact when successfully targeting younger patients and patients with channelopathies, and should include strategies to improve confidence in taking β -blockers and increasing beliefs around the necessity for β -blockers. We can take direction from successful interventions with other disease groups which have also shown adherence improves when regimens are simplified where possible,²⁵ depression is treated,²⁶ unhelpful illness and medication perceptions are addressed,^{22, 27} and barriers are addressed in follow-up interactions by allied health.²⁸

Table 3 Regression analysis for the combined adherence z-score

	B	SE B	β	95% CI for B	
				Lower bound	Upper bound
Step 1					
(Constant)	-0.860	0.270		-1.395	-0.325
Age	0.015	0.005	0.293*	0.005	0.024
Channelopathy vs cardiomyopathy	0.123	0.159	0.073	-0.192	0.439
Step 2					
(Constant)	-2.730	0.509		-3.738	-1.721
Age	0.007	0.004	0.139	-0.002	0.016
Channelopathy vs cardiomyopathy	0.033	0.142	0.020	-0.248	0.314
BMQ-necessity	0.039	0.015	0.236*	0.011	0.068
BMQ-concern	-0.014	0.017	-0.070	-0.047	0.019
MASES-R	0.586	0.132	0.430†	0.324	0.848
BIPQ-treatment control	-0.010	0.031	-0.028	-0.071	0.052
BIPQ-coherence	-0.008	0.031	-0.272	-0.070	0.053

* $p < 0.01$, † $p < 0.001$.

BIPQ, Brief Illness Perception Questionnaire; BMQ, Beliefs about Medicines Questionnaire; MASES-R, Medication Adherence Self-Efficacy Scale-Revised.

A Cochrane review published recently²⁸ encourages future adherence interventions to select non-adherent participants and use multidisciplinary approaches tailored to the individual's needs. The present study makes a first step in highlighting which groups of patients to focus on and what patient-centred variables could be included in such interventions.

Limitations

The current study has some limitations that should be noted. Although 34% is a common response rate for postal and web-based surveys,²⁹ it may limit the generalisability of the findings as it may not be representative of the population as a whole. This was highlighted by the substantial difference between the non-adherence rate found by this study (16%) compared with cardiac studies in general (40%) and the long QT syndrome study (51%), which used the same registry but assessed adherence with pharmacy records. The cause of this is possibly a response bias in that more non-adherent people chose not to participate, in which case the level of non-adherence found in this sample is likely an under-representation of non-adherence in the wider CID population. It could also be explained by methodological choices, in that adherence was measured using self-report in the current study. This can cause a socially desirable response bias for those who did participate in the study. There are definitely benefits to self-reports of adherence; they are relatively simple and inexpensive to use, and they can help identify reasons for a patient's non-adherence.³⁰ However self-report measures may result in an overestimation of adherence due to memory bias. Finally there were significant differences between participants and non-participants in terms of age and ethnicity, and due to the cross-sectional data causality cannot be determined.

CONCLUSIONS

Non-adherence to β -blockers is a significant issue in a population of patients with CID. Adherence is worse in younger people with cardiac ion channelopathies rather than cardiomyopathies. Psychological factors associated with non-adherence in this population include beliefs about medication, confidence in taking medication and illness perceptions. These findings present an opportunity to develop multidisciplinary interventions targeted to the correct subpopulation to improve adherence.

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Competing interests None declared.

Patient consent for publication Obtained.

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Data sharing statement As part of this study we collected information on anxiety and depression and risk perceptions and plan to publish papers on these topics. Data were collected with the ethics requirement that patients' data are confidential and will not be shared. However any questions should be directed to the corresponding author.

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