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Early View

Original article

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Asthma prescribing according to Arg16Gly beta-2 genotype: a randomized trial in adolescents

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Take Home Message

Personalized prescribing in adolescents with asthma demonstrated that beta-2 adrenoreceptor genotype directed treatment results in a small but significant improvement in PAQLQ. Beta-2 adrenoreceptor genotype guided treatment requires further investigation.

Abstract

Introduction The A allele of rs1042713 (Arg16 amino acid) in the beta-2 (β2) adrenoreceptor is associated with poor response to long-acting β2-agonist (LABA) in young people with asthma. Our aim was to assess whether the prescribing of second line controller with LABA or a leukotriene receptor antagonist (LTRA) according to Arg16Gly genotype would result in improvements in pediatric asthma-related quality of life questionnaire (PAQLQ).

Methods We performed a pragmatic randomized controlled trial (RCT) via a primary care clinical research network covering England and Scotland. We enrolled participants aged 12-18 years with asthma taking inhaled corticosteroids. A total of 241 participants (mean (SD) age 14.7 years (1.91)) were randomized (1:1) to receive personalized care (genotype directed prescribing) or standard guideline care. Following 4-week run-in participants were followed for 12-months. The primary outcome measure was change in PAQLQ. Asthma control, asthma exacerbation frequency and healthcare utilization were secondary outcomes.

Results Genotype directed prescribing resulted in an improvement in PAQLQ compared to standard care 0.16, (95%CI 0.00-0.31; p=0.049), although this improvement was below the pre-determined clinical threshold of 0.25. The AA genotype was associated with a larger improvement in PAQLQ with personalized versus standard care 0.42, (95%CI 0.02-0.81; p=0.041).

Conclusion This is the first RCT demonstrating that genotype driven asthma prescribing is associated with a significant improvement in a clinical outcome compared to standard care. Adolescents with the AA homozygous genotype benefited most. The potential role of such β2-

adrenoceptor genotype directed therapy in younger and more severe childhood asthma warrants further exploration.

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Genotype

Beta-2 gene polymorphysms

Paediatric asthma

Asthma clinical trials

Asthma Quality of life

Abbreviations

ACQ:	Asthma control questionnaire
ADRB2:	β2 adrenergic receptor
PAQLQ:	Pediatric asthma quality of life questionnaire
Arg:	Arginine
CI:	Confidence interval
CRN:	Clinical research network
GINA	Global Initiative for Asthma
Gly:	Glycine
HTA:	Health technology assessment
ICS:	Inhaled corticosteroids
IMD:	Index of Multiple Deprivation
LABA:	Long-acting β2 agonists
LTRA:	Leukotriene receptor antagonist
MCID:	Minimum clinically important difference
NiHR:	National institute for health research
PiCA:	Pharmacogenomics in childhood asthma
RCT:	Randomized controlled trial
SNP:	Single nucleotide polymorphism
TRuST:	Tayside randomisation system
UKCRN:	United Kingdom Clinical Research Network

Introduction

Asthma is the most common chronic condition affecting children [1]. It is associated with substantial health and quality of life burden for the patient as well as significant healthcare expenditure globally [2]. Childhood asthma is treated in a step-wise approach using controller medications, initially with inhaled corticosteroids (ICS) and if symptoms are not subsequently well controlled then addition of either inhaled long-acting β2 agonist (LABA) or a leukotriene receptor antagonist (LTRA), or by a further increase in ICS dose [3].

There is a wide degree of heterogeneity in response to treatment amongst young people with asthma, with estimates that 60-80% of the observed variance between individuals could be due to genetic differences [4]. There has been particular interest in a variation in the gene encoding for the β2 adrenergic receptor (*ADRB2*) at position 16 (rs1042713) resulting in an allelic substitution from glycine to arginine (Gly16Arg). The homozygous AA variant is found in approximately 15% of people and has been associated with poor response to ICS-LABA controller therapy in young people [5-7]. These findings have not been widely replicated in adult studies aside from the demonstration of greater bronchoprotective subsensitivity with the A allele in response to long acting β-agonist therapy [8-11]. It is hypothesized that, for young people with the A genotype, regular ICS-LABA use results in agonist induced down regulation and associated uncoupling of the β2 receptor thus impairing the efficacy of the medication [12, 13].

A meta-analysis from the Pharmacogenomics in Childhood Asthma (PiCA) consortium comprising 4226 children showed a 34% elevated risk of asthma exacerbation for each copy of the A allele in young people with ICS-LABA controller treatment, with at least one copy of A

allele being present in 62.8% of people [7]. One prospective study showed that use of a LTRA instead of LABA in young people homozygous for AA reduced school absence and improved asthma symptom and quality of life scores [14]. It is thus important to test whether Arg16Gly genotype directed therapy (personalized medicine) in adolescents with asthma leads to improvement in quality of life.

The principal aim was to test our hypothesis that prescribing of second line asthma controller medication (LABA or LTRA) according to Arg16Gly genotype compared to standard care provided according to the British Thoracic Society (BTS) guidelines would result in an improvement in quality of life determined by standardized pediatric asthma quality of life questionnaire (PAQLQ) in 12-18 year olds with asthma. Secondary aims included assessing the effect of genotype directed prescribing on: (i) asthma control (validated asthma control questionnaire (ACQ-6)); (ii) exacerbation frequency (requirement for oral steroids) and; (iii) health care utilization (non-routine primary-care review, emergency department attendance or hospital admission).

Some results have been previously reported in the form of an abstract [15].

Methods

Subjects

Our trial consisted of participants of either sex aged 12-18 years with: (i) a documented physician diagnosis of asthma; (ii) taking inhaled corticosteroid (ICS) with or without the additional second-line controllers (LABA or LTRA). The target population was adolescents

whose asthma was managed in primary care in England and Scotland. Exclusions were: (i) known contraindication to LABA or LTRA; (ii) On step 4 of BTS guidelines (e.g. use of theophylline based controller medication such as Uniphyllin); (iii) presence of other major airway or lung disease (other than asthma); (iv) pregnancy or lactation; (v) participation in another clinical trial; (vi) inability to provide saliva / buccal cells for genotyping.

Study design

For this two-arm pragmatic randomized controlled trial (RCT), participants were recruited from throughout England and Scotland. The study duration was 13-months, consisting of a 4-week run-in period and 12-months of follow-up.

Participants were principally recruited through primary care via the clinical research network (CRN) across England and Scotland as well as the patient databases BREATHE and PAGES. Informed consent and assent were obtained online or by telephone with follow-up written consent. The study followed the Children's Research Network standard operating procedures, Health Research Agency guidelines and the Nuffield Council on Bioethics: Ethical issues obtaining informed consent (2015). Participant's aged 12-18 consented independently whilst parental consent was sought in addition for those 15 years and younger. The trial was sponsored by the University of Sussex (approval December 2014) and ethical approval was obtained from the East of Scotland Research Ethics Committee (15/ES/0007, approval March 2015). The trial was registered on the UK Clinical Research Network (UKCRN) website with details made available to the public before the recruitment of the first participant. This trial is registered with ClinicalTrials.gov NCT02758873.

Participants were randomized 1:1 ratio to personalized care (rs1042713 SNP based prescribing) or standard care by a web-based system, TRuST (Tayside Randomisation SysTem). Participants were allocated as per block randomization with no stratification or minimization. The personalized care group were prescribed asthma controller medication on the basis of their Arg16Gly genotype, AA or AG receiving montelukast (LTRA) and GG receiving salmeterol (LABA). The standard care group were prescribed controller medication based on the current BTS guidelines. Neither group nor the study team was blinded to group allocation or prescribed medication.

Participants undertook a 4-week run-in period where they were asked to use only ICS as their controller medication at the previously prescribed dose. Reliever medication was used by each participant as required. Outcomes were measured at baseline, following completion of run-in and 3, 6, 9 and 12-months. Study questionnaires were completed online or over the phone. Medications were prescribed by the participant's GP.

Change to the asthma control questionnaire (ACQ-6) score was used to determine the participant's controller treatment with a score $\geq$1.0 [16] or need for oral corticosteroid triggering escalation. The personalized care group were prescribed asthma controller medication on the basis of their Arg16Gly genotype, AA or AG genotypes receiving LTRA and GG receiving LABA. The standard care group were prescribed controller medication based on the BTS guidelines. A stable or decrease in ACQ score resulted in continuation of current treatment.

DNA collection kits were posted to participants with instructions and a paid return envelope. Saliva samples were collected using a commercially available pot (GeneFiX^{TM} DNA saliva

collector, Isohelix.com). DNA was prepared with the Isohelix GeneFiX saliva prep DNA kit. DNA extraction and Arg16Gly genotype status was determined at the University of Dundee, Division of Population and Health Genomics, using TaqMan-based allelic discrimination assays on an ABI 7900 Sequence Detection System (Applied Biosystems, Foster City, USA) as previously described [17].

Outcomes

The primary outcome was the change in pediatric asthma quality of life questionnaire (PAQLQ) [18] from completion of the run-in to completion of the study at 12-months. Secondary outcomes were change in asthma control questionnaire (ACQ-6) score, health care utilization for asthma management (non-routine primary care review, emergency department attendance or hospital admission) as well as exacerbation frequency (courses of oral corticosteroid). Adverse events were recorded as per Health Research Authority guidelines.

Analysis

A change of 0.5 units on the PAQLQ is considered to represent the minimal clinically important difference (MCID) [19]. We expected to see a 0.25 improvement in PAQLQ at 12 months in the standard care group with the improvements estimated on the basis of genotype frequency with a projected improvement of: 0.5 in the GG (40%); 0.25 in the AG (35%) and 0 in the AA genotype (15%). The calculated sample size, in order to detect a clinically relevant threshold of 0.25 units (0.5-0.25=0.25) in the primary outcome of PAQLQ score (SD=1.0; alpha 0.05; 90% power) was 100 participants in each group. To allow for a 15% attrition rate, the recruitment target was increased to 120 participants in each group.

Analyses comparing personalized and standard care were completed as pre-specified in the statistical analysis plan. All analyses were performed on intention to treat population i.e. by group randomized. Data for continuous outcome measures were assessed for normality prior to analysis. Transformations of the outcome variables were used where necessary if they were not normally distributed. If data were normally distributed, outcome measures were assessed using mixed model repeated measure analysis, adjusted for the corresponding baseline values and group allocation as fixed effects. Models used all available data from the end of the run-in period. Where data was not normally distributed and could not be transformed into a normal distribution, data was analyzed using non-parametric methods. Subgroup analyses were performed on participants with the Arg16Gly status AA. A two-sided P value of <0.05 was taken to be significant for all analyses. SAS software (version 9.4, SAS Institute Inc. Cary, NC, USA) was used for all statistical analyses. PACT conforms to CONSORT 2010 guidelines on RCT reporting.

Results

Between February 9, 2016 and April 25, 2018, 247 participants were consented and 241 randomized before entering the 4-week run-in period (figure 1). Participants were randomized to either personalized care (n=121) or standard care (n=120) for their asthma controller therapy. Baseline demographics and clinical characteristics were broadly similar between those receiving personalized or standard care with a mean age of 14.7 years across the two groups (table 1). There are however important differences between the groups with a greater proportion of adolescents receiving ICS, LABA and LTRA combination therapy at baseline in the standard care group (15% vs 6.6%) indicating a possible increased asthma severity in this group, and a lower prevalence of the AA genotype in the personalized care group (9.9% vs

15.0%), possibly impairing the overall clinical benefit of personalized medication prescribing in this group.

Completion of the run-in period (ICS only) resulted in 0.1 mean improvement in PAQLQ compared to baseline in both groups. A mean improvement in PAQLQ total score compared to end of run-in was observed in both the personalized and standard care groups (table 2).

Prescription of asthma controller medication as per Arg16Gly genotype SNP status (personalized care) resulted in an improvement in mean PAQLQ compared to standard care (0.16, 95% CI 0.00-0.31; p=0.049; table 2; figure 2a; figure 3) however, the difference was below the pre-determined clinical threshold of 0.25. The PAQLQ domains of emotional function and activity limitation score had the greatest mean difference in change with personalized care.

Sub-group analysis of the children with the homozygous AA genotype (n=27) demonstrated an improvement in mean PAQLQ that exceeded the clinical threshold of 0.25 in those receiving personalized compared to standard care (0.42, 95% CI 0.02-0.813; p=0.04; table 2; figure 2b). There were no adverse or serious adverse events reported throughout the duration of the trial.

A total of 28 (11.6%) participants experienced an asthma exacerbation (requirement for oral steroids) during 12-month follow-up, with numerically lower rates reported in the personalized care (8.3%) compared to standard care group (15.3%) (p=0.08). There was also a trend toward increased time to exacerbation in the personalized care (225.7 days) compared to the standard care group (141.5 days) (p=0.102). There was a similar improvement in ACQ score from the end of run-in when mean change was compared in the personalized care (0.42) and standard care

groups (0.47) (p=0.18). There was no association between personalized asthma controller directed prescribing and health care utilization or the number of asthma medications prescribed with a small increase in the mean number prescribed in the personalized care (0.3) and standard care groups (0.2) (p=0.36) (table 3).

Discussion

The PACT study is the first prospective RCT assessing the efficacy of genotype-directed prescribing in adolescent asthma. Prescription of second line controller medication with LABA or LTRA according to Arg16Gly genotype resulted in a statistically significant improvement in primary clinical outcome of PAQLQ, although the magnitude of improvement amounted to 0.16 and was below the a priori clinical threshold of 0.25. The quality of life benefit seen in adolescents with the homozygous AA genotype was 0.42, exceeding the clinically significant PAQLQ threshold.

Our findings are consistent with the only previous trial conducted examining the effects of LABA in relation to Arg16Gly genotype in children. That proof-of-concept study focused on previously genotyped asthmatic children who were all homozygous for the AA variant. A total of 62 children were randomized to receive either ICS and LABA or ICS and LTRA and were followed-up for 12-months. Children treated with a LTRA compared to LABA had a clinically relevant mean improvement in PAQLQ scores amounting to 0.53 as well as reduced school absences and use of rescue medication in comparison to those treated with LABA. [14] In-keeping with these findings, adolescents with the AA homozygous genotype benefitted most from genotype-directed prescribing in our current study.

Both RCTs are underpinned by a large meta-analysis of observational studies comprising five childhood asthma cohorts demonstrating an increased risk of exacerbations with each copy of the A allele amounting to a 34% (95% CI 15-50) difference for asthmatic children treated with ICS-LABA therapy [7]. In this study, we report a non-significant numerical trend toward decreased exacerbation frequency in the genotype directed treatment group (8.3% vs. 15·3%, p=0.08). The low exacerbation frequency (11.6%) within our well-controlled population recruited for this study is a likely confounding factor as to why this well described association did not reach significance. A 2018 systematic review further assessed the role of Arg16Gly genotype variation on LABA response in asthma, confirming that the contribution of genetics to LABA response is more consistently shown in children compared to adults [20]. It is hypothesized that this could relate to the altered phenotype of children's asthma with a greater emphasis of atopy in its pathogenesis as well as reduced duration of chronic airway inflammation and airway wall rigidity [21]. It is thus possible that a greater mean improvement in PAQLQ could be achieved with this genotype-directed intervention in younger children, especially in those with more severe disease.

A conspicuous observation from the study was that both the personalized and standard care groups had improved PAQLQ and ACQ at final follow-up, this notable 'trial effect' is well described [22]. A component of this known as the 'care effect' could result from participants in both arms of the PACT trial having more regular face-to-face contact with primary care healthcare practitioners. The frequent telephone or e-mail communication with the study team as per the study protocol may have altered health behavior - the Hawthorne effect [23]. It is also conceivable that by virtue of regularly completing the PAQLQ and ACQ questionnaires adolescents may have developed improved asthma symptom awareness, promoting self-education about asthma, triggers and the benefits of controller treatment and improved

adherence. This, potential 'trial effect', may explain how the mean improvement in PAQLQ exceeded the MCID in both groups which may in-turn have contributed to a smaller than anticipated response to genotype-directed therapy.

Our study has some limitations. The lower than expected effect of personalized medicine on PAQLQ score could partly be explained by the excellent symptom control at baseline with very good PAQLQ and ACQ scores demonstrated, leaving limited room for further improvement. This explanation is supported by the large number of adolescents who did not experience an exacerbation (88.4%) and did not require any non-routine healthcare utilization for their asthma (71.4%) during 12-month follow-up. The good baseline control on ICS treatment following the run-in period resulted in 65% of adolescents in the personalized medicine group not actually experiencing specific genotype based prescribing e.g. add on of LABA or LTRA thus diminishing the possibility of the benefit of personalized begin proven. Future studies aiming to identify the potential role of Arg16Gly genotype directed therapy may require selective recruitment of children with poorly controlled asthma. Differences between the groups could also explain the lower than anticipated response to personalized treatment. The greater proportion of adolescents receiving ICS, LABA and LTRA combination therapy at enrolment in the standard care group (15% vs 6.6%) could indicate potentially increased disease severity at baseline. A further contributing factor could be the lower than anticipated number of adolescents with the significant AA genotype in the personalized medicine group (9.9%) compared to the standard care group (15%) and a previous large population meta-analysis (16.1%) [7].

Ideally, the criteria for asthma diagnosis should be defined in accordance with the Global Initiative for Asthma (GINA) guidelines and documented for each patient involved in the study.

By recruiting patients with a physician diagnosis of asthma from primary care, where there may not be routine access to spiromery or the capability to perform broncholdilator reversibility, the accuracy of asthma diagnosis is impaired which is a notable limitation. However, as the vast majority of adolescents with asthma are managed in this setting this approach assesses the pragmatic real world efficacy of personalised asthma prescribing. The lack of ethnic diversity within the study participants (88.8% Caucasian) is a potential limitation. There is however, reason to believe our results could be generalizable to other populations given the finding of increased rate of exacerbation with LABA use with presence of the A allele amongst cohorts of young people of differing ethnicities [7].

An important element of the PACT study is in relation to the novel study methodology employed, utilizing telephone and online contact for consent and data collection along with study directed prescribing through the patients' GP without direct face-to-face contact with study team members at any point. This is unique in the investigation of young people's asthma. Replication of this methodology may help investigators to conduct trials in a safe manner during the Covid-19 pandemic. The significant associated cost reduction has important implications for future research studies, with the cost per patient of $1495 for the PACT study substantially lower compared to a mean cost of $4630 per patient for RCT's funded by the NIHR (National Institute for Health Research) Health Technology Assessment (HTA) program between 2000-2005 [24].

Further areas need to be explored more fully to understand the potential value of Arg16Gly genotype directed prescribing in the treatment of children's asthma especially those with more severe disease. On the basis of our findings it is important to re-evaluate our study question in a less well-controlled sample including younger children with suggestions that the benefits of

Arg16Gly genotype based prescribing are more pronounced in this group. It is hoped that we will have a greater understanding following publication of the PUFFIN trial, an in progress multi-center Dutch study exploring Arg16Gly genotype based prescribing in 6-17 year-olds with asthma utilizing asthma control test as the primary outcome measure [25].

Conclusion

In this 12-month trial, asthma controller prescribing on the basis of Arg16Gly beta-2 receptor genotype resulted in a small but significant improvement in PAQLQ in adolescents compared to standard care, however this was below the expected clinical threshold. A clear benefit was demonstrated for those with the AA homozygous genotype (15% of the population). We recommend further prospective randomized studies to help identify the potential clinical utility of personalized prescribing in young people's asthma.

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Figure legends

Figure 1 - Trial profile

Figure 2a - Pediatric asthma quality of life questionnaire total score

Data represented includes the median, 25th centile, 75th centile, lowest value and highest value. PAQLQ – Pediatric Asthma Quality of Life Questionnaire.

Figure 2b - Pediatric asthma quality of life questionnaire total score for A/A genotype

Data represented includes the median, 25th centile, 75th centile, lowest value and highest value. PAQLQ – Pediatric Asthma Quality of Life Questionnaire.

Figure 3 - Pediatric Asthma quality of life questionnaire total score change from baseline to 12 months follow-up

MCID – minimum clinically important difference

Table 1 – Baseline demographics and clinical characteristics

	Personalized care N=121	Standard care N=120
Age, years	14.6 (1.95)	14.7 (1.87)
Sex		
Male	57 (47.1%)	52 (43.3%)
Female	64 (52.9%)	68 (56.7%)
Genotype		
GLY/GLY (G/G)	53 (43.8%)	48 (40%)
ARG/GLY (A/G)	54 (44.6%)	53 (44.2%)
ARG/ARG (A/A)	12 (9.9%)	18 (15%)
Missing*	2 (1.7%)	1 (0.8%)
Ethnicity		
White	111 (91.7%)	103 (85.8%)
Black	0 (0%)	3 (2.5%)
Asian	1 (0.8%)	3 (2.5%)
Other	9 (7.4%)	11 (9.2%)
Baseline medications		
ICS	78 (64.5%)	79 (65.8%)
ICS + LABA	30 (24.8%)	19 (15.8%)
ICS + LTRA	5 (4.1%)	4 (3.3%)
ICS + LABA + LTRA	8 (6.6%)	18 (15%)
Healthcare use in previous month	14 (11.6%)	16 (13.3%)

* Participants withdrew from the study without providing saliva specimen

Data are mean (SD) or n (%)

ICS - Inhaled corticosteroid, LABA - Long-acting β2-agonist, LTRA - leukotriene receptor antagonist

Table 2 – Pediatric asthma quality of life questionnaire (PAQLQ) score change

	End of run-in values Personalized Standard	12 month values Personalized Standard	Mean change Personalized Standard	Overall mean difference in change * 95% CI	P value
PAQLQ total score	5.97 (5.80-6.14) 5.84 (5.65-6.02)	6.44 (6.31-6.57) 6.32 (6.19-6.45)	0.45 (0.27-0.63) 0.46 (0.28-0.65)	0.16 (0.00-0.31)	**0.049**
PAQLQ emotional function score	5.91 (5.71-6.10) 5.69 (5.47-5.90)	6.44 (6.32-6.56) 6.22 (6.06-6.39)	0.53 (0.35-0.72) 0.53 (0.33-0.73)	0.23 (0.04-0.42)	**0.02**
PAQLQ environment stimuli score	5.88 (5.65-6.10) 5.82 (5.60-6.04)	6.42 (6.25-6.59) 6.35 (6.18-6.52)	0.50 (0.26-0.74) 0.49 (0.26-0.73)	0.12 (-0.08-0.32)	0.25
PAQLQ activity limitation score	6.21 (6.07-6.35) 6.08 (5.91-6.24)	6.60 (6.49-6.71) 6.50 (6.38-6.61)	0.36 (0.21-0.51) 0.41 (0.25-0.57)	0.14 (0.00-0.28)	**0.04**
PAQLQ symptom score	5.81 (5.62-6.01) 5.67 (5.46- 5.89)	6.30 (6.13-6.47) 6.19 (6.03-6.34)	0.48 (0.25-0.72) 0.48 (0.24-0.71)	0.16 (-0.02-0.33)	0.08
PAQLQ total score (A/A)	5.59 (4.99-6.20) 5.77 (5.12-6.42)	6.54 (6.12-7.00) 6.36 (6.14-6.59)	0.92 (0.4-1.44) 0.64 (0.06-1.22)	0.42 (0.02-0.81)	**0.04 ****

Data are mean and 95% CI unless otherwise indicated.

PAQLQ – standardized pediatric asthma quality of life questionnaire.

* adjusted for treatment, genotype and baseline values.

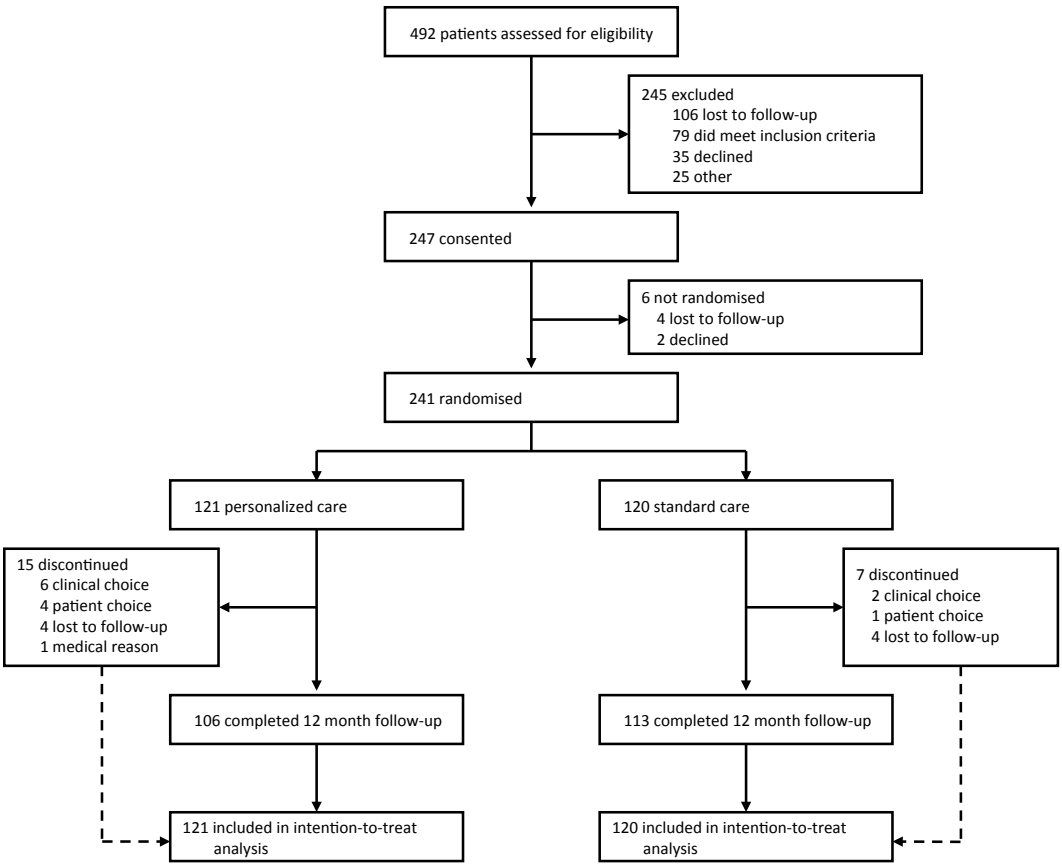
** adjusted for treatment, genotype, baseline values and SAP characteristics (sex, age, site and Index for Multiple Deprivation (IMD))

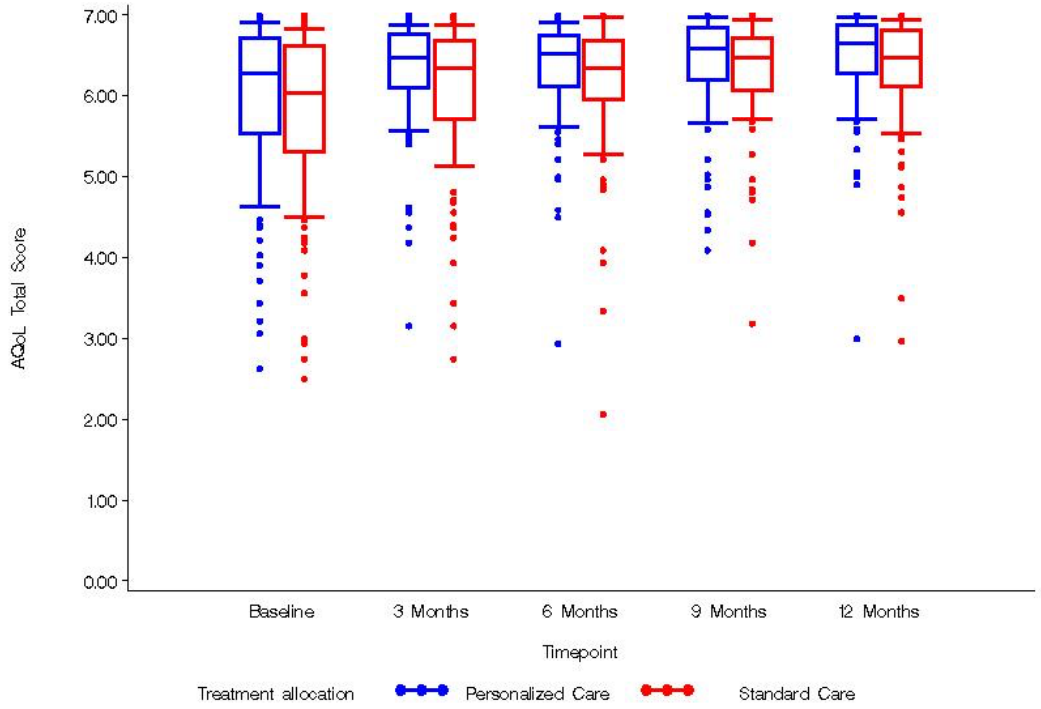
Table 3 – Secondary outcomes measures

	Personalized care	Standard care	Overall mean difference in change* Hazard Ratio (95% CI)	p-value
Any exacerbation, number (%)	10 (8.3%)	18 (15.0%)	0.52 (0.24-1.36)	0.10
Time to first exacerbation, days	225.7 (121.3-330.1)	141.5 (78.7-204.3)	2.11 (0.91-4.87)	0.08
No health care utilization, number (%)	87 (71.9%)	85 (70.8%)	0.98 (0.56-1.72)	0.73
Number of medications, mean change	0.3 (0.15-0.42)	0.2 (0.07-0.29)	1.71 (0.85-3.45)	0.36
ACQ-6, mean change	-0.42 (-0.60-0.42)	-0.47 (-0.66-0.27)	-0.10 (-0.25-0.05)	0.18

Data are mean (SD) or n (%).

PAQLQ – standardized pediatric asthma quality of life questionnaire.


492 patients assessed for eligibility
245 excluded
106 lost to follow-up
79 did meet inclusion criteria
35 declined
25 other
247 consented
6 not randomised
4 lost to follow-up
2 declined
241 randomised
121 personalized care
120 standard care
15 discontinued
6 clinical choice
4 patient choice
4 lost to follow-up
1 medical reason
7 discontinued
2 clinical choice
1 patient choice
4 lost to follow-up
106 completed 12 month follow-up
113 completed 12 month follow-up
121 included in intention-to-treat analysis
120 included in intention-to-treat analysis


7.00
6.00
5.00
4.00
3.00
2.00
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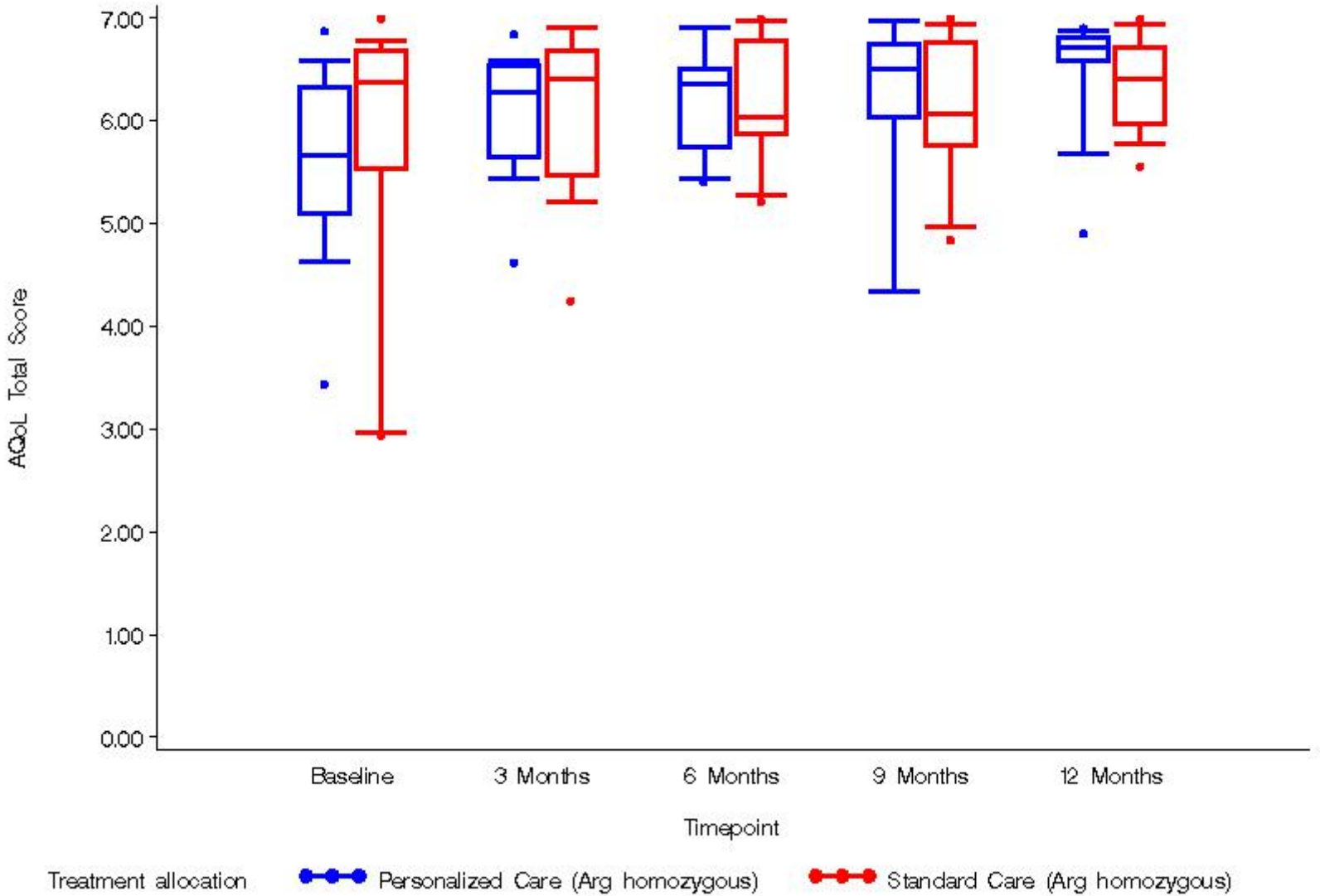
AQoL Total Score
Baseline
3 Months
6 Months
9 Months
12 Months
Timepoint
Treatment allocation
Personalized Care
Standard Care


7.00
6.00
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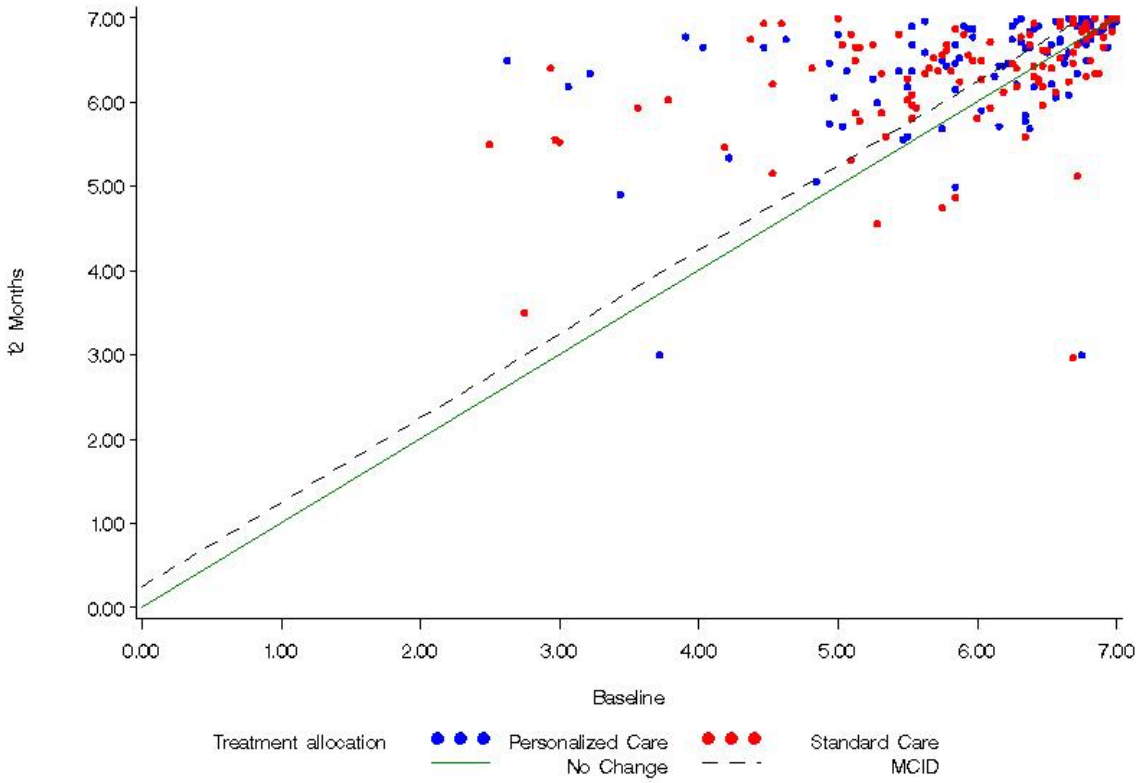
4.00
3.00
2.00
1.00
0.00
AQoL Total Score
Baseline
3 Months
6 Months
9 Months
12 Months
Timepoint
Treatment allocation
Personalized Care (Arg homozygous)
Standard Care (Arg homozygous)


12 Months
7.00
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2.00
1.00
0.00
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
Baseline
Treatment allocation
Personalized Care
Standard Care
No Change
MCID

Online Data Supplement

Asthma prescribing according to Arg16Gly beta-2 genotype: a randomized trial in adolescents

Tom Ruffles MD[1], Christina J Jones PhD[2], Colin Palmer PhD[3], Steve Turner MD[4], Jonathan Grigg MD[5], Roger Tavendale PhD[3], Fiona Hogarth MD[6], Petra Rauchhaus[7], Kristina Pilvinyte[6], Romanie Hannah MD[1], Helen Smith MD[8,9], Roberta Littleford PhD[10], Brian Lipworth MD[11], Somnath Mukhopadhyay PhD[1,3]

Inclusion and Exclusion Criteria

Inclusion criteria

a. Parent/Guardian/Participant is willing and able to give informed consent/assent

b. Physician-diagnosed asthma

c. Aged 12-18

d. Taking inhaled corticosteroids (ICS) with/without second line controllers (i.e. LABA and/or LTRA)

Exclusion criteria

a. Participant/Parent/Guardian is unwilling or unable to give informed consent/assent

b. Participant has to be assessed as competent to provide consent.

c. Known contraindication to montelukast or salmeterol

d. On step 4 asthma control medication e.g. taking Theophylline, Slo-phylin, Uniphyllin

e. Other major airway or lung disease, e.g. chronic lung disease of prematurity, cystic fibrosis, and abnormal airway anatomy

f. Pregnant or lactating females (if participants become pregnant during the course of the study they will be asked to inform the research team and be withdrawn from the study)

g. Participating in another clinical trial (other than observational trials and registries) concurrently or within 30 days prior to screening for entry into this study

h. Unable to provide saliva/buccal cells for genotyping