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ORIGINAL RESEARCH

Process Evaluation of a Double-Blind Randomized Controlled Trial to Assess the Efficacy and Safety of a Quadruple Ultra-Low-Dose Treatment for Hypertension Within a Federally Qualified Health Center Network (QUARTET USA)

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BACKGROUND: This convergent parallel-design mixed-methods process evaluation of the QUARTET USA (Quadruple Ultra-Low-Dose Treatment for Hypertension USA) clinical trial (NCT03640312) explores patient and health care professional perceptions about the use of low-dose quadruple therapy (LDQT) as a novel strategy for hypertension management.

METHODS AND RESULTS: A survey of all 62 patients enrolled in the QUARTET USA trial was conducted. A subsample of 13 patients and 11 health care professionals, recruited via purposive sampling, took part in semistructured interviews. At enrollment, 68% of participants (mean [SD] age, 51.7 [11.5] years; 56% self-identified as Hispanic: Mexican ethnicity, 16% as Hispanic: other ethnicity, 16% as Black race, 8% as White race, and 1.6% as South Asian race) reported that their current health depended on blood pressure medications, and 48% were concerned about blood pressure medications. At trial completion, 80% were satisfied with LDQT, 96% were certain the benefits of taking LDQT outweighed the disadvantages, and 96% reported that LDQT was convenient to take. Both patients and health care professionals found LDQT acceptable because it reduced patients' perceived pill burden and facilitated medication adherence. Health care professionals stated that a perceived limitation of LDQT was the inability to titrate doses. Steps to facilitate LDQT implementation include introducing stepped-care combinations and treatment protocols, inclusion in clinical practice guidelines, and eliminating patient cost barriers.

CONCLUSIONS: LDQT was an acceptable strategy for hypertension treatment among patients and health care professionals involved in the QUARTET USA clinical trial. Although LDQT was generally perceived as beneficial for maintaining patients' blood pressure control and facilitating adherence, some clinicians perceived limitations in titration inflexibility, adverse effects, and costs.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03640312.

Key Words: fixed-dose combination therapy ■ hypertension ■ low-dose quadruple therapy ■ qualitative research ■ QUARTET USA (Quadruple Ultra-Low-Dose Treatment for Hypertension USA) clinical trial

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CLINICAL PERSPECTIVE

What Is New?

- To our knowledge, this is the first mixed-methods study embedded within a randomized controlled trial (QUARTET USA [Quadruple Ultra-Low-Dose Treatment for Hypertension USA]) investigating the use of a low-dose quadruple therapy strategy on hypertension control rates within an urban federally qualified health center network.
- Low-dose quadruple therapy was well accepted for trial participants and clinicians involved in the clinical trial: high treatment satisfaction was achieved in a patient population composed of a large proportion of Mexican American immigrants with mostly offsetting views on the *necessity* and *concerns* about blood pressure medications at study enrollment.

What Are the Clinical Implications?

- In the United States, scalable interventions are needed to address inequitable blood pressure control rates across diverse contexts.
- Patients and clinicians identified better medication adherence and lower patient pill burden as benefits of low-dose quadruple therapy that may facilitate improved blood pressure control.
- Health care professionals would prescribe low-dose quadruple therapy if clinical trial evidence supports its efficacy and if patient cost barriers are eliminated.

Nonstandard Abbreviations and Acronyms

ACCESS	Access Community Health Network
BMQ	Beliefs About Medicines Questionnaire
FDC	fixed-dose combination
LDQT	low-dose quadruple therapy
QUARTET	Quadruple Ultra-Low-Dose Treatment for Hypertension
SBP	systolic blood pressure
SPRINT	Systolic Blood Pressure Intervention Trial
TSQM v1.4	Treatment Satisfaction Questionnaire for Medication

It is estimated that >1.1 billion individuals globally (24% of adult men and 20% of adult women) have elevated blood pressures (≥140/90 mm Hg).[1] Reducing systolic blood pressure (SBP) by 10 mm Hg can reduce stroke risk by 41% and coronary heart disease risk by 22%.[2] SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated that a target SBP of <120 mm Hg significantly reduced all-cause mortality by 27% when compared with a target SBP of <140 mm Hg (standard approach) in individuals with high cardiovascular disease risk.[3,4] These results led to the 2017 American Heart Association/American College of Cardiology guideline to recommend a target SBP <130 mm Hg for patients eligible for pharmacotherapy. However, in the United States, hypertension awareness, treatment, and control rates were suboptimal and inequitable before 2017,[5] and control rates worsened with lower blood pressure targets. Thus, strategies to reduce blood pressure effectively, efficiently, equitably, and safely to SPRINT-like levels are urgently needed.

Fixed-dose combination (FDC) therapy is a highly scalable public health strategy to prevent morbidity and mortality associated with cardiovascular disease globally.[6–9] FDC therapy increases long-term medication adherence and reduces the amount of physician visits required by reducing the need to up-titrate therapy (ie, overcoming therapeutic inertia).[6,8–11] However, despite the potential large-scale public health benefits of an FDC-based treatment strategy, the concept has yet to achieve widespread implementation.[6,9,12] Qualitative data are needed to explore why FDC for hypertension control has had poor uptake despite strong evidence supporting its use, including elucidating any patient- and clinician-specific hesitancies beyond simple availability (eg, cost and inflexible titration).[13]

QUARTET (Quadruple Ultra-Low-Dose Treatment for Hypertension) Australia, a 12-week randomized, double-blind active controlled trial that enrolled 591 patients, demonstrated that mean SBP was lower by 6.9 mm Hg and blood pressure control rates were higher among patients treated with low-dose quadruple therapy (LDQT) (76%) compared with patients treated with standard monotherapy (58%).[14] The study results suggest LDQT to be safe and well tolerated.[14] Trial participants largely identified as White race (82%), and 23% had received government support for health care expenditures.[14] Therefore, the effects of antihypertensive medications across drug classes may be additive,[15] but this hypothesis requires further investigation in randomized, controlled trials across diverse contexts.

QUARTET USA is a companion 12-week randomized trial that was conducted at 2 health centers within Access Community Health Network (ACCESS), a network of federally qualified health centers (FQHCs) in the United States, and funded by the National Heart, Lung, and Blood Institute (NCT03640312). This trial investigated whether treatment with LDQT containing candesartan, 2 mg, amlodipine, 1.25 mg, indapamide, 0.625 mg, and bisoprolol, 2.5 mg, once daily, achieved blood pressure control more effectively, and with fewer adverse effects

at 12 weeks, compared with standard monotherapy with candesartan, 8 mg, once daily.[16] In this report, we present the findings of the QUARTET USA clinical trial process evaluation, which explores patient and health care provider perceptions about LDQT as a novel strategy for hypertension treatment. Understanding patient-centered mechanisms of the LDQT strategy is important for achieving widespread blood pressure control.

METHODS

Data and Code Sharing

Quantitative data and code will be made available through the Biologic Specimen and Data Repository Information Coordinating Center at the National Heart, Lung, and Blood Institute, which can be accessed at: https://biolincc.nhlbi.nih.gov/home/. Qualitative data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

This study was a convergent parallel-design mixed-methods evaluation including patients living with hypertension and health care professionals involved in the QUARTET USA clinical trial. Participants were recruited from ACCESS in Chicago, IL, which provides primary care to 170 000 low-income individuals and families, including >27 000 individuals with hypertension, across 35 health centers. Quantitative surveys were completed by all participants enrolled in the QUARTET USA clinical trial (n=62 total participants; 32 in the intervention arm and 30 in the comparator arm) at the time of enrollment, and at 6- and 12-week follow-up visits. The qualitative study was completed by 13 trial participants and 11 health care professionals recruited via purposive sampling from the 2 ACCESS health centers involved in the QUARTET USA clinical trial. Patients were interviewed at varying times after completing their final assessment at the health centers (average, 7.9 months [SD, 7.1 months]). Health care professionals were interviewed between January 2022 and June 2022, depending on their availability. This study received institutional review board approval from Northwestern University. All interview participants provided either written or audio-recorded informed consent for interviewing and recording. A translated version of the informed consent document was provided for Spanish-speaking participants.

Data Collection

Quantitative

Participants who completed the quantitative surveys comprised the total number of individuals enrolled in the QUARTET USA trial. Beliefs about medicines were captured at baseline and 12 weeks using the Beliefs About Medicines Questionnaire (BMQ),[17] whereas data on treatment satisfaction were captured at 6 and 12 weeks by the Treatment Satisfaction Questionnaire for Medication (TSQM v1.4; IQVIA RDS, Inc).[18] A validated translated Spanish version of the TSQM v1.4 was provided by IQVIA.[19] The BMQ is used to predict adherence[20] and has been validated in a Spanish-speaking patient population in the United States receiving care at FQHCs.[21] Other clinical trials have used the BMQ to predict medication adherence in Hispanic/Latino patient populations with uncontrolled hypertension.[22] The data were collected in English and Spanish by trained interviewers following a standardized protocol. The interviewers were part of the trial investigator team but were masked to randomized group allocation. The trial was conducted between August 2019 and May 2022.

Qualitative

We conducted semistructured interviews with questions based on the realist framework,[23] which seeks to understand which interventions work, for whom, and under which circumstances (context-mechanism-outcome framework).[24,25] Interviewers followed a topic guide for both clinician and patient interviews to ensure consistency in the topics explored during the interviews. The interview guides were adapted from a previous process evaluation of a multicenter pragmatic randomized, controlled trial of a cardiovascular-based polypill strategy in Australian primary care.[23] Details of the interview guides are provided in Table S1. A pilot health care professional interview was conducted in August 2019, and the remaining interviews were conducted between February 2020 and July 2022.

Interviews were conducted over Zoom by 1 of 3 study investigators (O.A.S., T.J., and A.Q.). O.A.S. has extensive experience in conducting qualitative research and led the coding and analyses stages. All health care professional interviews were conducted in English. Patient interviews were conducted in English (n=7) and Spanish (n=6). One interviewer (A.Q.) is fluent in Spanish and conducted interviews with Spanish-speaking participants. The duration of interviews ranged from 20 to 60 minutes. We informed participants about the aims of the study, and the stated goal was to understand clinician experiences of implementation and patient experiences on adverse effects, adherence, and trust with clinical care in the QUARTET USA trial. None of the participants dropped out, and we did not return transcripts or results to participants for comments.

Statistical Analysis

Quantitative

Patient and clinician characteristics were summarized as frequency and percentage and mean (SD) values.

Cross-tabulations were used to show the variations in patients' responses to BMQ and TSQM v1.4 scales by intervention arms. Mann-Whitney *U* tests were used to compare distribution of domain scores for TSQM v1.4 by intervention arm. Wilcoxon signed-rank tests for matched pairs were used to evaluate change in domain scores for BMQ scales between baseline and follow-up. To avoid possibility of biased estimates for the BMQ scales, missing data were computed with 10 imputations using chained equations.[26] The number and percentage of patients with missing data for the BMQ scales are reported in Table S2. A 2-sided $P<0.05$ was used to define statistical significance. The analyses were exploratory, and we did not adjust for multiple hypotheses tests. The statistical analyses were performed in STATA, version 14.[27]

Qualitative

All interviews were recorded and transcribed verbatim by a third-party service in May 2022 (QualTranscribe, Mesa, AZ). The interviews in Spanish were translated and transcribed into English by QualTranscribe. For quality assurance, the same Spanish-speaking team member (A.Q.) who conducted the original interviews reviewed the transcripts in Spanish for technical and conceptual accuracy. Transcripts were redacted for confidentiality and uploaded to Dedoose v9.0.17 software for coding and analyses.[28] Transcribed interviews were read multiple times by study members for familiarization. Transcripts were analyzed thematically using both a deductive approach (ie, using the realist framework) and an inductive approach (eg, based on emerging themes from the data). The codebook was modified using the constant comparative method. Coding was conducted by the 3 study investigators who conducted the interviews (O.A.S., T.J., and A.Q.). O.A.S., T.J., and A.Q. collaboratively developed the codebook by first coding 3 patient and provider transcripts together to agree on key themes. N.R.K. reviewed the initial codebook and provided feedback. The remaining transcripts were divided between the 3 study investigators for independent coding and were cross-checked and discussed by at least 1 other study investigator (O.A.S., T.J., or A.Q.). We adhered to the Consolidated Criteria for Reporting Qualitative Research guidelines.[29]

Integration of Quantitative and Qualitative Results

Common themes from the quantitative survey data and the qualitative study were integrated in the discussion. The integration was done by matching the themes in the BMQ and TSQM v1.4 with interview themes, and coherence of the findings was assessed by confirmation (when both quantitative and qualitative results reinforced each other), expansion (when divergence existed to address different aspects of the phenomenon), and discordance (when both sources contradicted each other).[30]

RESULTS

Participant Characteristics

Quantitative Results of QUARTET USA Trial Participants

Table 1 shows the baseline characteristics of the patients. A total of 62 patients participated in the trial (mean [SD] age, 51.7 [11.5] years; 34 [55%] men; 35 [56%] self-identified as Hispanic: Mexican ethnicity, 10 [16%] self-identified as Hispanic: other ethnicity, 11 [18%] self-identified as Black race, 5 [8%] self-identified as White race, and 1 [1.6%] self-identified as South

Table 1. Baseline Patient Characteristics

Characteristic	Value (n=62)
Age, mean (SD), y	51.7 (11.5)
Sex	
Male	34 (54.8)
Female	28 (45.2)
Race or ethnicity	
Hispanic: Mexican	35 (56.5)
Hispanic: other	10 (16.1)
Black	11 (17.7)
White and South Asian*	6 (9.7)
Country of birth	
United States	21 (33.9)
Other†	41 (66.1)
Education	
Less than high school	25 (40.3)
High school and above	37 (59.7)
Employment status	
Unemployed	30 (48.4)
Employed	32 (51.6)
Marital status	
Not married	26 (41.9)
Married/living with partner	36 (58.1)
Insurance status	
Uninsured	30 (48.4)
Insured	32 (51.6)
SBP, mean (SD), mm Hg	138.1 (11.2)
DBP, mean (SD), mm Hg	84.3 (10.5)

Data are given as number (percentage) unless otherwise indicated. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

*Low cell counts.

†Among those born outside the United States (n=41; 66% of trial participants), 34 participants (82.9%) were born in Mexico, and 7 participants (17.1%) were born in the following countries: Guatemala, Venezuela, Argentina, Columbia, and India.

Asian race). Mean (SD) baseline SBP was 138.1 (11.2) mm Hg, and mean (SD) baseline diastolic blood pressure was 84.3 (10.5) mm Hg.

Quantitative Results of Interview Participants

We interviewed 13 trial participants (mean [SD] age, 55.5 [9.9] years; 6 [46.2%] men; 8 participants self-identified as Hispanic [Mexican and other] ethnicity [61.5%], 3 self-identified as Black/sub-Saharan African descent [23.1%], and 2 self-identified as White race [15.4%]). Eight participants (61.5%) were born in the United States, and 5 (38.5%) were born outside the United States. Seven participants had less than high school education; 4 participants were uninsured. Seven participants were from the intervention arm, and 6 were from the comparator arm. Mean (SD) baseline SBP was 142.4 (12.7) mm Hg, and mean (SD) baseline diastolic blood pressure was 84.4 (10.6) mm Hg.

In addition, we interviewed 10 health care professionals (7 women). Three (30%) self-identified as Black race, 2 (20%) self-identified as White race, 2 (20%) self-identified as South Asian race, and 1 (10%) self-identified as Hispanic ethnicity. Two health care professionals (20%) did not disclose their race and ethnicity. Mean (SD) age of the health care professionals interviewed was 38.9 (12.6) years, with 11.3 (9.9) years in practice. Health care professionals included 5 physicians, 4 nurse practitioners, and 1 physician associate.

Beliefs About Medicines and High Blood Pressure

In the quantitative survey, Table 2 shows that the percentage of patients who believed in the necessity of their medication for maintaining health was relatively high (scores more than scale midpoint; Table S3). Specifically, similar proportions of patients at baseline (68%) and 12-week follow-up (66%) mentioned that their health at present depended on blood pressure medications. The proportion of patients who reported that blood pressure medications worried them was relatively high at baseline (48%) and follow-up (52%). In general, patients had mostly offsetting views on the necessity and concerns of blood pressure medications at baseline and follow-up (necessity-concerns differential of 2.1; Table 3). Most patients did not believe that blood pressure medications disrupted their daily lives. Although >40% of patients believed that they should stop their medications every now and then, <1 of every 5 (18% at baseline and 13% at follow-up) believed that their medications do more harm than good. Generally, there was no difference in patients' beliefs about medicines at baseline and at follow-up (Table 3). A sensitivity analysis was performed by imputing missing values,

Table 2. Respondents Agreeing/Strongly Agreeing With BMQ Statements at Baseline and 12-Week Follow-Up

Domain	Baseline (n=62)	12-wk follow-up (n=54)
Necessity scale		
My health at present depends on blood pressure medicines	42 (67.7)	36 (66.7)
My life would be impossible without blood pressure medication	27 (43.6)	23 (42.6)
Without blood pressure medication, I would become very ill	32 (51.6)	26 (48.2)
My health in the future will depend on my medicines	29 (46.8)	31 (57.4)
Blood pressure medication protects me from becoming worse	40 (64.5)	30 (56.6)
Concerns scale		
Having to take blood pressure medication worries me	30 (48.4)	28 (51.9)
I sometimes worry about the long-term effects of blood pressure medication	37 (59.7)	29 (53.7)
Blood pressure medication is a mystery to me	28 (45.2)	24 (45.3)
Blood pressure medication disrupts my life	2 (3.2)	2 (3.7)
I sometimes worry about becoming too dependent on my blood pressure medication	25 (40.3)	26 (48.2)
General: overuse		
Physicians use too many medicines	13 (21.0)	13 (24.1)
Physicians place too much trust on medicines	31 (50.0)	31 (57.4)
If physicians had more time with patients, they would prescribe fewer medicines	12 (19.4)	16 (29.6)
General: harm		
People who take medicines should stop their treatment for a while every now and again	28 (45.2)	23 (42.6)
Medicines do more harm than good	11 (17.7)	7 (13.0)

Data are given as number (percentage). BMQ indicates Beliefs About Medicines Questionnaire.

Table 3. Scale Means and SDs for BMQ Scales at Baseline and 12-Week Follow-Up

Domain	Mean (SD)		Z	*P* value*
	Baseline (n=53)	12-wk follow-up (n=53)		
Necessity†	17.0 (3.8)	16.7 (3.7)	0.59	0.55
Concerns†	14.9 (3.5)	14.6 (3.6)	0.69	0.49
General overuse‡	9.5 (1.6)	9.8 (1.5)	−1.48	0.14
General harm§	5.5 (1.7)	5.5 (1.7)	0.00	>0.99
Necessity-concerns differential	2. (4.4)	2.1 (4.6)	−0.24	0.81

BMQ indicates Beliefs About Medicines Questionnaire.
*Wilcoxon signed-rank test result for matched pairs. Nine patients had missing values on baseline and follow-up and were not included in this analysis.
†Scores range from 5 to 25, with higher scores indicating stronger agreement with the concept represented by the scale.
‡Scores range from 5 to 15, with higher scores indicating stronger agreement with the concept represented by the scale.
§Scores range from 5 to 10, with higher scores indicating stronger agreement with the concept represented by the scale.

and the overall results match up after the analysis was repeated (Table S4).

Treatment Satisfaction

Table 4 shows that treatment satisfaction (measured at the 12-week follow-up) was not significantly different between patients randomized to the intervention or comparator groups. Overall, there was a high level of global satisfaction and perceived convenience among all study participants: 80.4% of patients were satisfied with the LDQT, 96.4% were confident that taking LDQT was a good thing for them, 96.4% were certain the benefits of taking LDQT outweighed the disadvantages, and 94.6% reported that it was convenient to take (Table S5). In addition, >90% of patients reported that LDQT was easy to use in its current form, easy to plan when the medication would be used, and convenient to take the medication as instructed (Table 5).

Fifteen patients (26.8%) reported that they experienced some adverse effects because of taking the study drug (Table S5), and 4 participated in the interviews. Among the 15 patients who experienced adverse effects, 93.3% stated that the adverse effects of taking the medication were bothersome to them, more than half reported that the adverse effects of the study drug interfered with their physical health (53.3%), and all mentioned that the adverse effects of the study drugs interfered with their mental function and overall satisfaction with the medication (Table 5).

Table 4. Scale Means and SDs for TSQM v1.4 by Intervention Arm at Trial Completion

Domain	Mean (SD)		Z	*P* value*
	Comparator (n=26)	Intervention (n=30)		
Effectiveness†	13.2 (3.3)	13.1 (3.2)	0.33	0.74
Adverse effects‡	14.5 (1.0)	13.4 (2.1)	0.80	0.42
Convenience§	10.9 (2.5)	11.3 (2.6)	−0.86	0.39
Global satisfaction‖	12.8 (3.4)	13.3 (3.2)	−0.56	0.58

TSQM v1.4 indicates Treatment Satisfaction Questionnaire for Medication.
*Mann-Whitney *U* test for independent samples.
†Scores range from 7 to 21, with higher scores indicating stronger agreement with the effectiveness of low-dose quadruple therapy.
‡Scores range from 5 to 20, with higher scores indicating higher bothersome of low-dose quadruple therapy adverse effects. Dichotomized item, not scored.
§Scores range from 7 to 21, with higher scores indicating stronger agreement with convenience of low-dose quadruple therapy.
‖Scores range from 5 to 17, with higher scores indicating stronger agreement with convenience of low-dose quadruple therapy.

Theme 1: Context for LDQT Use in an FQHC Patient Population

Clinician Experience, Perceived Benefits, and Shortcomings of FDC Therapy

The qualitative findings showed that most health care professionals (10 of 11) had experience with prescribing FDC therapy for hypertension. Seven health care professionals had experience with prescribing FDC therapy for other chronic conditions, such as diabetes. Health care professionals discussed several perceived benefits of FDC therapy for managing high blood pressure, including the potential to reduce adverse reactions because it includes lower doses of the individual medications and reduces the need for maximizing monotherapy. Health care professionals also commented on how FDC aligns with patient preferences to reduce pill burden and improves medication adherence.

> *Compliance, probably because instead of having to take 3 different medicines in the day or 4, you can take 1, if you can roll them off. But usually, for me it's 2 pills. Occasionally, like I said, 3 pills, then 1. But just having to take 1, it's just more convenient for the patients, better compliance, then sometimes better control with the combination than taking them separately. (Health Care Professional 7).*

Table 5. Respondents Satisfied, Very Satisfied, and Extremely Satisfied With TSQM v1.4 at Trial Completion by Intervention Arm

Domain	Comparator (n=26)	Intervention (n=30)
Effectiveness		
How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?	22 (84.6)	25 (83.3)
How satisfied or dissatisfied are you with the way the medication relieves your symptoms?	21 (80.8)	25 (83.3)
How satisfied or dissatisfied are you with the amount it takes the medication to start working?	22 (84.6)	25 (83.3)
Adverse effects		
As a result of taking this medication, do you experience any adverse effects at all?	6 (23.1)	9 (30.0)
How bothersome are the adverse effects of the medication you take to treat your condition?*	5 (83.3)	9 (100.0)
To what extent do the adverse effects interfere with your physical health and ability to function (ie, strength and energy levels)?*	3 (50.0)	5 (55.6)
To what extent do the adverse effects interfere with your mental function (ie, ability to think clearly and stay awake)?*	6 (100.0)	9 (100.0)
To what degree have medication adverse effects affected your overall satisfaction with the medication?*	6 (100.0)	9 (100.0)
Convenience		
How easy or difficult is it to use the medication in its current form?	25 (96.2)	29 (96.7)
How easy or difficult is it to plan when you will use the medication each time?	25 (96.2)	28 (93.3)
How convenient or inconvenient is it to take the medication as instructed?	25 (96.2)	28 (93.3)
Global satisfaction		
Overall, how confident are you that taking this medication is a good thing for you?	25 (96.2)	29 (96.7)
How certain are you that the good things about your medication outweigh the bad things?	25 (96.2)	29 (96.7)
Taking all things into account, how satisfied are you with this medication?	20 (76.9)	25 (83.3)

Data are given as number (percentage). TSQM v1.4 indicates Treatment Satisfaction Questionnaire for Medication.
*Among those experiencing adverse effects.

Health care professionals also stated that FDC therapy for hypertension has shortcomings. Some health care professionals reported that FDC therapies were often not covered by insurance and may be unaffordable for patients with low socioeconomic status. Health care professionals reported concerns about inflexibility of FDC-based dosing regimens and difficulty identifying culprit medications in the setting of adverse effects. In addition, some health care professionals expressed concern that FDC therapy might increase the number of adverse reactions.

> *Let's say, if the patient has high blood pressure, starting the fixed-dose medication, what do you do? Do you have any dose adjustment, or how does it work? I don't know this part… Let's say the patient systolic blood pressure dropped from 160 down to 150 or 140, but we still have room to decrease the blood pressure, what is going to be the next step? Will we increase the dose, or will we add another medication? (Health Care Professional 2).*

Facilitators of Medication Adherence

Trust in health care professionals and strong clinician-patient rapport were dominant themes in factors that facilitate adherence to antihypertensive medications. These themes were driven by clinicians taking the time to address any medication concerns.

> *I trust a lot in doctors and the people who are inside the circle, when they tell me 'Okay, you have this, and you have to take this for this, because this is going to help you. This—' and that's it. (Patient 9).*

Minor themes included patient-facing strategies (eg, using a pillbox and use of alarms), clinician-led strategies (eg, including the patient in treatment decisions and recommending home blood pressure monitoring), health care delivery strategies (eg, using a mail delivery service, providing clinic transportation, offering telehealth, and ensuring insurance coverage), and societal factors (eg, race-gender congruence) (Table S6).

Barriers to Medication Adherence

Health care professionals described limited patient education and pill burden as important barriers in adherence to antihypertensive medications. For example, several health care professionals commented on difficulty engaging patients in understanding why they are taking antihypertensive medications, especially if they are on multiple medications and if their blood pressure appears well controlled.

> *And I know that one of the most [important] barriers is education, […] the importance of why they are taking the medication. Even if blood pressure is okay, why they need to continue. (Health Care Professional 10).Another thing is just education, and really getting the patient engaged to understand why they're taking it, especially when they're on so many medications. They always think that if they're on all these multiple medications, then it's actually doing them more harm than good. (Health Care Professional 6).*

The cost of antihypertensive medications was another barrier to medication adherence identified by most clinicians. There was a perception that newer medications are more expensive. Both patients and clinicians commented on the chronicity of hypertension and the need to be on lifelong antihypertensive therapy.

> *Some people are afraid like, 'I know once I start this medication, I'm never going to be able to come off.' Or they're worried once they start one, it's going to escalate and they're going to have to take a lot of medications. (Health Care Professional 9).*

Some patients commented on the desire to take purportedly "natural" medicines (eg, herbs and cannabidiol), discussed the perception that pharmaceutical drugs cause more harm, and expressed greater interest in continuing lifestyle changes instead of initiating medications. Clinicians identified barriers related to distrust of the medical system for historically marginalized communities, but this concern was not commonly expressed by participants (Table S6, Facilitators of Medication Adherence: Trust in Health Care Professionals). Several clinicians noted that patients who have long work schedules, night shifts, or physically demanding jobs often forget to take their medications.

Theme 2: Mechanisms of LDQT

Overall Acceptability of LDQT

Many patients and clinicians reported that LDQT was acceptable and perceived as a beneficial medication because it reduced pill burden, improved blood pressure control, and was smaller in size based on its manufacturing. Patients particularly felt comfortable taking the medication and were willing to continue taking it if it were made available and prescribed by their primary care physicians.

> *Well, I was happy, and I was comfortable, also the confidence they made me feel, I don't have any negative comments about it (LDQT). I am fine, and I liked having participated, because I was able to see that my blood pressure could improve. (Patient 11).*

Adverse Effects

Most patients reported that they did not experience serious adverse effects attributable to taking the study drug. Two patients, however, mentioned that they experienced lower heart rate, dizziness, and constipation for a short time after taking the study drug.

Theme 3: Outcomes of LDQT Use

Effectiveness of LDQT

Most participants mentioned that LDQT improved medication adherence and improved blood pressure.

> *I went to see my doctor during my annual checkup, and she said to me: 'It is perfect, you keep on with it because your blood pressure is wonderful,' because I gave her the blood pressure records I was taking in the morning and at night. I gave her the record and she said: 'That works very well with you, keep on with it because it is giving you a good result'; it was giving me good results, too bad it ended. (Patient 12).Well, I didn't do anything different. I just took 1 pill a day at a certain time, 1 every day. It was easier to take 1 than to take 4 or 5. (Patient 8).*

Increasing LDQT Reach

Clinicians identified health insurance coverage as the most important priority for ensuring LDQT is widely affordable and available to all patients regardless of socioeconomic status.

> *I'm not quite sure how this works for a newer medication, but if the larger public health insurance companies could buy in*

and provide this medication at a low cost, that would be huge, especially in the community where I work, where a lot of the ACCESS health centers are. If this medicine is beneficial, the studies are out there and if the different Medicaid groups offer it, then that would be super helpful. (Health Care Professional 8).

Clinicians also mentioned that getting patients to share their experiences (eg, word of mouth and patient testimonials) on the positive impact of the LDQT on their blood pressure control would expand LDQT reach in underserved populations.

Increasing LDQT Adoption Among Health Care Professionals

Clinicians stated that obtaining health insurance coverage (eg, Medicaid managed care plans) and inclusion in the 340B drug discount program, along with the need to demonstrate a strong clinical evidence base, were the most important priorities for increasing adoption among health care professionals.

I have a lot of patients on Medicaid, so if it was covered by Medicaid, I definitely think I would use it. Depending on the results of the study, of course. But we've been excited about this, we've been wanting to hear about this. I think we first heard about the study maybe 4 years ago, so we've been waiting a while to start the study, and now… we're just waiting on the results. It really all depends on insurance, and that's the main thing. If the insurance doesn't cover it, then people either have to pay out of pocket, or they have to pay a higher copay if we're able to get the insurance to do a prior authorization for it. (Health Care Professional 7).Well, I have patients that I would try to transition, especially if they're on multiple medications in those same families, that I would prefer to use 1 medication versus 2 or 3, so that we could have better adherence. But again, with the population that I serve, I would hope that maybe, again, if it is approved, that it would be part of like the 340B program, so that it would be available to my patient population. (Health Care Professional 6).

Health care professionals also commented that LDQT would have to show a better long-term adverse effect profile compared with the standard of care before they can use the medication in their clinical practice.

We're evidence-based clinicians, or we should be, right? So, I think, should the research from this trial and from other trials come out and say, long-term data shows that side effects, safety profile, all of that is much greater with using this medication versus using the standard of care… I think that would be something I would gladly implement into my practice. Right now, obviously it's in the research stages. So… I would still likely use a lower dose of a monotherapy over something like this. (Health Care Professional 1).

Furthermore, clinicians stated that inclusion of LDQT into future national hypertension guidelines would increase LDQT adoption. Other strategies described by clinicians include peer-to-peer education and presentations on the effectiveness, safety, and titration of LDQT at health center meetings and at scientific conferences.

Theme 4: Trial Implementation

Transitioning Patients From LDQT to Routine Care

Most health care professionals reported that they did not experience any concerns with transitioning patients from the LDQT to routine blood pressure medications after the trial, and this was partly attributable to the effective study coordination.

It was really smooth. I think this may have been due in part… to the site coordinator that was seeing my patients. But I think she did a really good job of saying, 'Okay, you were on this medication before. I'm scheduling an appointment with your PCP, to see if you should be taking X medication again.' She was very specific about sending them. 'This was your previous prescription. Please, ask specifically about this when you go back.' So, most of my patients came back saying, 'I used to be on amlodipine. Should I take that again?' (Health Care Professional 8).

However, 1 clinician expressed concerns about the difficulty of getting his/her patient back to appropriate blood pressure–lowering medication after the trial ended. The clinician also stated that it was difficult communicating the transition to his/her patient because of the positive impact of LDQT on blood pressure control.

> *Because they (patients) were like, well, why can't I take the other medication? Like, well, because we have to try to get it approved first, all that stuff. So, I think it was kind of just the education of them trying to understand why they couldn't continue to be on it, especially because it helped control their blood pressure. (Health Care Professional 6).*

DISCUSSION

Evidence suggests LDQT, involving multiple low-dose antihypertensive medications in 1 pill, achieves superior blood pressure control for initial or early hypertension management compared with usual care or monotherapy.[11,14,15] To foster widespread implementation and scale-up, it is essential to understand patient and health care professional perceptions about the acceptability and adoption of LDQT. Using a convergent parallel-design mixed-methods study embedded within the QUARTET USA clinical trial, we found that LDQT was well accepted by patients and health care professionals in an FQHC setting, and that patients were satisfied with treatment. We also identified facilitators and barriers to acceptability, adoption, and adherence.

In this study, LDQT was generally well accepted among study participants and health care professionals. High treatment satisfaction, as measured by the TSQM v1.4 at study completion, was achieved in a patient population with mostly offsetting views on the *necessity* and *concerns* about blood pressure medications (BMQ) at baseline. These findings support results of prior qualitative studies that indicated an increasing acceptance of prescribing FDC therapy, provided there is proof of effectiveness, and it is affordable for patients.[23,31–33]

Most clinicians were willing to implement LDQT use into their everyday clinical practice if supported by clinical research, covered by Medicaid managed care plans, and included in the federal 340B drug discount program. Nearly all clinicians interviewed had experience with prescribing FDC and perceived its benefits on hypertension control. However, despite familiarity with prescribing FDC for hypertension and diabetes, clinicians expressed hesitancy in managing adverse effects and up-titrating LDQT if initial dosing fails to achieve sufficient blood pressure lowering. Therefore, developing treatment algorithms for LDQT, including introducing stepped-care combinations, and providing additional guidance on managing adverse effects, would be beneficial in increasing adoption.

For antihypertensive FDCs, a change in the product landscape may be needed to improve conversion of real-world treatment patterns with FDC-equivalent options.[13] Notably, this was not a barrier discussed by health care professionals in this study. In addition, overcoming therapeutic inertia with greater initial (ie, upfront) blood pressure lowering was not mentioned as a perceived benefit of LDQT (or antihypertensive FDCs) among clinicians in this study, although this is 1 of the main aims of an LDQT strategy.[14] This suggests low awareness on using antihypertensive FDCs as initial or early treatment of hypertension to overcome therapeutic inertia among health care professionals involved in the QUARTET USA clinical trial. A paradigm shift in primary care medical education is likely needed to promote an initial ultra-low-dose FDC antihypertensive strategy with stepwise dose increases compared with a monotherapy-dependent initial management strategy requiring frequent titrations.[12]

There were also mixed clinician views on whether LDQT would increase or decrease adverse effects compared with standard-dose monotherapy. Although the quantitative findings showed that ≈1 of every 4 patients (27%) were satisfied with the adverse effects of LDQT, 4 of 13 patients interviewed for the qualitative study mentioned that they experienced minor adverse effects. These findings suggest that LDQT has a favorable safety profile from the patient perspective, which was corroborated in the main trial findings (NCT03640312) and in the QUARTET Australia results.[14]

Clinicians believed that LDQT increased medication adherence by reducing pill burden. Trial participants further commented on mechanisms facilitating increased adherence, including smaller physical pill sizes and reduced pill burden, clinician-patient communication and trust, more frequent and close monitoring by study staff, and the use of home blood pressure monitoring. In line with prior research,[34,35] health care professionals mentioned that 1 of the facilitators of adherence is clinicians taking the time to address patients' concerns and questions about medications, adverse effects, and other concerns raised by patient. Therefore, to increase adherence to antihypertensive medications, there is a need for improved counseling strategies and a focus on health literacy.

Studies have shown that FDC therapy improves patient medication adherence.[36–38] On the other hand,

medication adherence can be attenuated if patients must pay higher out-of-pocket costs.[39,40] Hence, removing patient cost barriers, as suggested by patients and health care professionals, may increase LDQT widespread implementation and scale-up. In addition to medication cost, transportation is another patient-level barrier. The QUARTET USA trial provided transportation for study participants to the participating health centers. However, ACCESS has a much wider network of neighborhood health centers closer to where patients live and work, which could facilitate scaling FDC to more sites and patients. Addressing multilevel barriers will be essential for enhancing the spread and scale of antihypertensive FDCs in the United States.

Prior process evaluations of FDCs, including polypills, for cardiovascular disease have highlighted several dominant themes. A qualitative study of the UMPIRE (Use of a Multidrug Pill in Reducing Cardiovascular Events) trial suggested that medication adherence improved more in the polypill group compared with usual care, especially among participants who had lower baseline adherence, including high-risk primary prevention participants.[41] Similarly, a qualitative study of the KGAP (Kanyini Guidelines Adherence With the Polypill) trial (Australia) suggested that the use of a polypill may be best suited for high-risk primary prevention.[23] The primary mechanisms facilitating increased adherence were simplification of the medication regimen (convenience and reduced pill burden)[23,41] and cost savings.[23] Major perceived limitations of cardiovascular polypills included inflexibility of dosing regimens and difficulty identifying culprit medications in the setting of adverse effects.[23] Both perceived limitations were also mentioned by health care professionals in the current study.

Strengths and Limitations

A major strength of the QUARTET USA clinical trial is that it was inclusive of a diverse patient population whose perspectives are underrepresented in cardiovascular clinical trials.[42] QUARTET USA comprised a large proportion of self-identified Hispanic individuals of Mexican heritage, with 82% of those born outside the United States (n=42, 66% of all participants) reporting Mexico as their country of birth. QUARTET USA was perceived favorably by health care professionals involved in the study because it built the capacity to conduct future randomized controlled trials at FQHCs (Table S6, Mechanisms). The acceptability of clinical trial research at community health centers highlights the importance of making future clinical research more inclusive and representative of the broader population, given that there are critical gaps in best practices to implement evidence-based care for Hispanic/Latino individuals and other underrepresented groups.[43–45]

This study has several important limitations. First, the qualitative sample was not representative of all patients and health care professionals in the trial because of purposive sampling. The QUARTET USA clinical trial comprised a large percentage of self-identified Mexican American immigrants (54.8%). Our qualitative study interviewed 7 (54%) participants who self-identified as Hispanic-Mexican, which closely resembles the actual proportion represented in the clinical trial. Therefore, our findings related to beliefs about medications may not be generalizable to other Hispanic/Latino subgroups and other race and ethnic groups because of undersampling of these populations and the diversity and heterogeneity in cultural beliefs, values, and risk factors for cardiovascular disease between Hispanic and Latino subgroups.[46,47]

We also acknowledge the possibility that health care professionals included in the qualitative study may not be representative of the wider population of clinicians at FQHCs across the United States. These health care professionals identified and referred potential patients to the QUARTET USA clinical trial, and their views and overall awareness may have been more favorable toward using FDC therapy (LDQT) for hypertension control.

For the qualitative study, we achieved data saturation for interviews of health care professionals but not for interviews of clinical trial participants.[48] This was attributable to pandemic restrictions, lack of participant engagement, and competing priorities at FQHC partner sites. Thus, the small patient sample size in the qualitative investigation may have prevented the identification of additional or divergent themes. Nevertheless, our findings offer important insights into the perceptions of this specific underserved patient population. Interviews were conducted several months after trial completion and via Zoom, which may have contributed to recall bias and less detailed responses from some of the patients and exclusion of patients with limited access to technology.[49] Despite these limitations, the findings suggest patients and health care professionals recognize LDQT as a potential strategy to improve hypertension management in underserved patient populations. Future qualitative work should seek to further explore barriers and facilitators to the implementation and scale-up of antihypertensive FDCs (including LDQT) across diverse contexts.

CONCLUSIONS

This convergent parallel-design mixed-methods study provides an in-depth evaluation of the relevance of LDQT for patients and health care professionals as a novel strategy for hypertension management. Generally, LDQT was well accepted among patients

and health care professionals because it improved patients' blood pressure control with a favorable safety profile from the perspective of those in this study. Our results suggest that widescale and equitable adoption of LDQT will require introducing stepped-care combinations at different doses, developing treatment protocols, and minimizing patient cost barriers, including insurance coverage and transportation costs.

ARTICLE INFORMATION

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Dr Huffman has received travel support from the American Heart Association and World Heart Federation and consulting fees from PwC Switzerland for activities outside this research. Dr Huffman has an appointment at The George Institute for Global Health, which has a patent, a license, and has received investment funding with intent to commercialize fixed-dose combination therapy through its social enterprise business, George Medicines. Dr Huffman has pending patents for heart failure polypills. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S6

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