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ORIGINAL ARTICLE

Achieving optimal adherence to medical therapy by telehealth: Findings from the ORBITA medication adherence sub-study

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Abstract

Introduction: The ORBITA trial of percutaneous coronary intervention (PCI) versus a placebo procedure for patients with stable angina was conducted across six sites in the United Kingdom via home monitoring and telephone consultations. Patients underwent detailed assessment of medication adherence which allowed us to measure the efficacy of the implementation of the optimization protocol and interpretation of the main trial endpoints.

Methods: Prescribing data were collected throughout the trial. Self-reported adherence was assessed, and urine samples collected at pre-randomization and at follow-up for direct assessment of adherence using high-performance liquid chromatography with tandem mass spectrometry (HPLC MS/MS).

Results: Self-reported adherence was >96% for all drugs in both treatment groups at both stages. The percentage of samples in which drug was detected at pre-randomization and at follow-up in the PCI versus placebo groups respectively was: clopidogrel, 96% versus 90% and 98% versus 94%; atorvastatin, 95% versus 92% and 92% versus 91%; perindopril, 95% versus 97% and 85% versus 100%; bisoprolol, 98% versus 99% and 96% versus 97%; amlodipine, 99% versus 99% and 94% versus 96%; nicorandil, 98% versus 96% and 94% versus 92%; ivabradine, 100% versus 100% and 100% versus 100%; and ranolazine, 100% versus 100% and 100% versus 100%.

Conclusions: Adherence levels were high throughout the study when quantified by self-reporting methods and similarly high proportions of drug were detected by urinary assay. The results indicate successful implementation of the optimization protocol delivered by telephone, an approach that could serve as a model for treatment of chronic conditions, particularly as consultations are increasingly conducted online.

Abbreviations: CAD, coronary artery disease; HPLC MS/MS, high-performance liquid chromatography with tandem mass spectrometry; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

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KEYWORDS
cardiovascular diseases, chromatography, liquid, coronary artery disease, medication adherence, therapeutics

1 | INTRODUCTION

Achieving optimal medication adherence in cardiovascular medicine is an enormous clinical challenge and a longstanding priority for global health.[1] Poor adherence to medical therapy in the cardiovascular disease prevention setting is unsurprisingly associated with adverse cardiovascular outcomes.[2] Adherence to therapy, even in patients enrolled in a clinical trial has been shown to be as low as 60%.[3] In clinical practice, achieving good adherence in primary prevention has been more challenging than for secondary prevention.[4] In recent years, a multitude of varying telehealth and mobile health interventions have been studied which largely share a common purpose of encouraging patient engagement in self-monitoring and self-management, however with varying success.[5] Face-to-face counselling and team-based hypertension care have been shown to have good outcomes.[6,7] The ORBITA (Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty for stable angina) trial showed that the increment in exercise capacity following percutaneous coronary intervention (PCI) was lower than expected and not statistically different to the effect of a placebo procedure in patients with stable coronary artery disease (CAD) on a background of optimal medical therapy (OMT).[8] Some commentators highlighted that optimization of medical therapy in ORBITA was intensive and could not be easily replicated in clinical practice.[9] Indeed, in clinical practice, guideline-directed medication optimization prior to PCI is variable. Analysis of the CathPCI registry in the USA in 2011 showed that OMT (defined as aspirin, statin, a beta-blocker or documented intolerance) was achieved in just 44% of patients prior to PCI.[10] A Canadian registry study in 2014 showed that OMT (defined in this instance as statin, beta-blocker, and either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker) was achieved in only 33.9% of patients prior to PCI.[11] ORBITA was conducted in the UK, where targets for heart rate and blood pressure were achieved in less than 50% of patients when optimizing anti-anginal therapy prior to elective PCI.[12] In spite of international guidelines for conduct of clinical trials recommending quantification of adherence in trial protocols, the practice is not widespread.[13] Prior to ORBITA, adherence to medical therapy was not assessed in trials of PCI and medical therapy until the COURAGE trial,[14] which quantified adherence using the Morisky score, a widely-used subjective method of assessment expressed on an ordinal scale.[15] Therefore, no preceding trial of PCI and medical therapy has used a direct method of assessment of adherence. In ORBITA, the trial patients were expected to achieve optimization in a short, intensive period to ensure that patients did not experience undue delays in accessing PCI compared to usual clinical care. In addition to documentation of patterns of prescribing, patients' self-reported adherence to therapy and urine samples for direct detection of urinary metabolites were collected. In this way, the efficacy of the medical therapy protocol and possible treatment imbalances between the groups that could affect the main study endpoints could be assessed. Quantifying adherence in detail also allowed evaluation of any changes in medication taking behavior that may have arisen following PCI.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients aged 18–85 years with stable angina attributable to single-vessel coronary artery disease were eligible to participate. Patients were excluded if they had previous coronary bypass surgery, left main coronary artery stenosis, contraindications to drug-eluting stent use, chronic total occlusion, severe valvular heart disease, severe left ventricular systolic impairment, moderate-severe pulmonary hypertension, life expectancy less than 2 years, or were unable to consent.

2.2 | Study design and organization

Detailed medication prescribing and adherence assessments were carried out on all ORBITA participants (Figure 1). Once enrolled patients entered the 6-week medication optimization phase. Once this phase had been completed no further optimization of therapy took place. Patients then travelled to the study coordinating centre, Imperial College Healthcare NHS Trust, London, UK, for further clinical assessment including cardiopulmonary exercise testing and dobutamine stress echocardiography. The research protocol coronary angiogram was carried out at their local center a short few days later, during which they were randomized to either PCI or a placebo procedure. After 6-weeks of blinded follow-up, during which no further treatments were offered and no study visits took place, patients returned for repeat testing and study unblinding at the coordinating center. A favorable review of the study protocol was obtained from the London Central Research Ethics Committee and the trial received support from the NIHR Imperial Biomedical Research Centre, Foundation for Circulatory Health, Imperial College Healthcare Charity, Philips Volcano, NIHR Barts Biomedical Research Centre.

2.3 | Personnel

Two research fellows were essential to the study team and had distinct predefined roles. The unblinded fellow (RAL) provided support in the catheterization laboratory for the randomization procedure

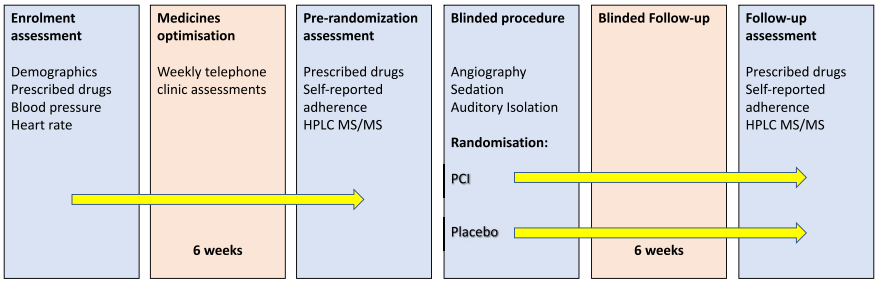

FIGURE 1 Study flow diagram. Demographics and prescribed drugs were recorded at enrolment and patients were provided with a home blood pressure monitor and shown how to carry out home readings. Patients were asked to keep diary entries of these readings for review during scheduled telephone clinic assessments which took place 1–3 times weekly during the 6-week optimization phase. At pre-randomization, patients attended the study coordinating center where a final check of their prescribed drugs was done along with self-reported adherence for each drug and patients were asked to give a urine sample for detection of drug using the HPLC MS/MS method. Patients then returned to their local center a few days later for the randomized study procedure, after which no further changes to therapy took place and no further study visits took place. At the follow-up assessment prescribed drugs, a repeat of the pre-randomization assessments was done. HPLC MS/MS – high-performance liquid chromatography with tandem mass spectrometry, PCI – percutaneous coronary intervention

and in doing so became unblinded to the randomized treatment assignment. The blinded fellow (DT) remained so throughout the study and performed all pre-randomization and follow-up tests. RAL was based primarily in the coronary catheter laboratory and was responsible for enrolling new patients to the study as well as providing support to the site teams. RAL was the main clinical point of contact for patients from enrolment and throughout the medication optimization phase until after randomization. This enabled RAL to engage patients at enrolment and give instructions regarding standardized recording of home blood pressure, provide medication prescriptions and resolve issues with dispensing. RAL scheduled weekly telephone reviews with patients for introduction and titration of cardiovascular preventive and anti-anginal therapy. DT encountered patients for the first time at the pre-randomization assessment visit in London and became the main clinical point of contact for patients in the blinded follow-up period. DT was not involved in medication optimization but carried out a final check of protocol adherence before the patients proceeded to randomization. The authors confirm that the PI for this study is Professor Darrel Francis and that he had direct clinical responsibility for patients.

2.4 | Remote clinical assessments and optimization of medical therapy

Initial contact between the patient and the study team was face-to-face. During this encounter patients were provided with a home blood pressure monitor and shown how to use the monitor appropriately. The study team then created a patient profile on the study electronic record system and scheduled weekly telephone clinic assessment encounters with the unblinded fellow (RAL). Thereafter all patient encounters took place remotely. Patients were asked to keep a daily record of home blood pressure and heart rate readings for review during the weekly telecall. In some instances, where tighter control was indicated patients had up to three tele-health reviews per week. In line with conventional clinical guidelines for management of stable angina the study protocol stipulated a target heart rate of 60/min and target blood pressure of 140/90 mmHg.[16–18] The electronic record system could be accessed online from any location using a standard web browser, allowing patient reviews to take place while the study fellow moved between sites and without the need for patients to travel to clinic. During the initial encounter patients were provided with a prescription for the protocol listed drugs. Prescriptions were adjusted to achieve targets for blood pressure and heart rate during these sessions. Troubleshooting of issues with prescribing, dispensing, medication intolerances or any other need of change of drug were all managed remotely.

2.5 | Endpoints

2.5.1 | Self-reported adherence

Self-reported adherence was assessed for each medication by asking each patient "How many days in the preceding week did you take this medication?"[19] This was carried out at pre-randomization and at follow-up. Self-reported adherence was not measured in the first 42 consecutive patients as it was introduced following a protocol amendment.

2.5.2 | Direct assessment of medication adherence

Direct assessment of medication adherence was carried out using high performance liquid chromatography-tandem mass spectrometry (HPLC MS/MS) for detection of protocol-directed medications (Table 1) in urine samples at both pre-randomization and at follow-up stages. Samples were analyzed as described previously at the National Centre for Adherence Testing, University Hospitals of Leicester NHS Trust.[20] Briefly, samples were aliquoted and stored at −70°C on receipt. Samples were prepared prior to analysis by

TABLE 1 ORBITA medical therapy protocol drugs detectable by HPLC MS/MS

Drug	
Aspirin	Not screened
Other antiplatelet agents	
Clopidogrel	Screened
Prasurgel	Not screened
Ticagrelor	Not screened
Atorvastatin	Screened
Perindopril	Screened
Bisoprolol	Screened
Amlodipine	Screened
Isosorbide mononitrate	Not Screened
Nicorandil	Screened
Ivabradine	Screened
Ranolazine	Screened

dilution (to detect polar compounds) and by extraction (to detect non-polar compounds). They were analyzed using an Agilent Technologies 1290 Series High Pressure Liquid Chromatograph interfaced with an Agilent Technologies 6460 Triple Quadrupole Mass Spectrometer fitted with a jet-stream electrospray ionization source. Medications were identified by the unique mass to charge ratio of the parent compound or metabolite. The method is qualitative (yes/no) with detection limits between 1 and 200 ng/mL. We have demonstrated that the variable pharmacokinetic parameters of a medication do not affect relative detection or non-detection.[21] The biochemical screening methodology was not able to detect aspirin, prasugrel, ticagrelor nor isosorbide mononitrate. Hence, the adherence status for these compounds was not quantified (Table 1). Data are not available for the first 5 randomized patients.

2.6 | Analysis

We present descriptive statistics for prescribed drug as a percentage of number of patients at each stage, self-reported adherence scores, and percentages of detected drug present in the tested samples. Self-reported adherence scores were calculated from the number of days in the previous 7 that the patient remembered to take that medicine. The average self-reported adherence scores per drug are presented. Similarly, with regard to the direct assessment of adherence results we present averages for detected drug as a percentage of those samples.

3 | RESULTS

The baseline characteristics of the ORBITA participants are shown in Table 2. The groups were evenly balanced and prescribing data were available for all 200 randomized participants. Self-reported adherence data and HPLC MS/MS urinalysis data were present for 158 and 195 patients, respectively.

TABLE 2 Baseline characteristics

	PCI (*n* = 105)	Placebo (*n* = 95)	All (*n* = 200)
Age (years)	65·9 (9·5)	66·1 (8·4)	66·0 (9·0)
Male	74 (70%)	72 (76%)	146 (73%)
BMI (kg/m^2)	28·0 (4·7)	29·5 (5·1)	28·7 (5·0)
Diabetes	15 (14%)	21 (22%)	36 (18%)
Hypertension	72 (69%)	66 (69%)	138 (69%)
Hyperlipidemia	81 (77%)	62 (65%)	143 (72%)
Current smoker	11 (10%)	15 (16%)	26 (13%)
Previous myocardial infarction	5 (5%)	7 (7%)	12 (6%)
Previous PCI	10 (10%)	15 (16%)	25 (13%)
Left ventricle systolic function			
Normal	98 (93%)	85 (89%)	183 (92%)
Mild impairment	3 (3%)	7 (7%)	10 (5%)
Moderate impairment	4 (4%)	3 (3%)	7 (4%)
CCS class			
I	2 (2%)	3 (3%)	5 (3%)
II	64 (61%)	54 (57%)	118 (59%)
III	39 (37%)	38 (40%)	77 (39%)
Angina duration (months)	9·5 (15·7)	8·4 (7·5)	9·0 (12·5)

Patient characteristics at enrolment. Data are presented as mean (SD). BMI, body mass index; CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention.

3.1 | Optimization of medical therapy

At enrolment, prior to optimization, 82 (78%) and 75 (79%) of patients in the PCI and placebo groups, respectively, were prescribed aspirin, 71 (68%) and 66 (69%) patients were prescribed a statin and 20 (19%) and 28 (29%) patients were prescribed ≥2 anti-anginal agents. By pre-randomization which signifies the end of OMT (Table 3) 102 and (97%) and 92 (97%) patients were prescribed aspirin, 100 (95%) and 91 (96%) were prescribed atorvastatin or other statin and 90 (86%) and 93 (98%) patients were prescribed ≥2 anti-anginal agents, in the PCI and placebo groups, respectively. Most patients were prescribed two anti-platelet agents, in keeping with guideline-directed clinical practice for elective PCI. The most commonly prescribed, protocol-directed anti-anginal agents were calcium channel blockers—prescribed for 95 (90%) patients that received PCI and 87 (92%) patients that received placebo. Prescription of anti-anginal agents was evenly balanced between the groups, both at pre-randomization and at follow-up and there was no notable change in prescribing from pre-randomization to follow-up within groups.

TABLE 3 Adherence to OMT by self-report and HPLC MS/MS

	Enrolment		Pre-randomization						Follow-up					
	PCI (*N* = 105)	Placebo (*N* = 95)	PCI (*N* = 105)			Placebo (*N* = 95)			PCI (*N* = 105)			Placebo (*N* = 95)		
	Prescribed (%)	Prescribed (%)	Prescribed	Self-reported [days (%)]	HPLC MS/MS detected	Prescribed	Self-reported [days (%)]	HPLC MS/MS detected [% samples tested]	Prescribed	Self-reported [days (%)]	HPLC MS/MS detected	Prescribed	Self-reported [days (%)]	HPLC MS/MS detected [% samples tested]
Aspirin	82 (78%)	75 (79%)	102 (97%)	6.95 (99.29%)	–	92 (97%)	6.86 (98.00%)	–	103 (98%)	6.93 (99.00%)	–	91 (96%)	6.81 (97.29%)	–
Clopidogrel	40 (38%)	36 (38%)	102 (97%)	7.00 (100.00%)	66 (96%)	88 (93%)	7.00 (100.00%)	52 (90%)	102 (97%)	6.97 (99.57%)	91 (98%)	88 (93%)	6.84 (97.71%)	68 (94%)
Other AP	2 (2%)	4 (4%)	3 (2%)	7.00 (100.00%)	–	6 (6%)	7.00 (100.00%)	–	3 (3%)	7.00 (100.00%)	–	6 (6%)	6.75 (96.43%)	–
Atorvastatin	49 (47%)	47 (49%)	88 (84%)	6.82 (97.43%)	82 (95%)	86 (91%)	7.00 (100.00%)	68 (92%)	86 (82%)	6.83 (97.57%)	72 (92%)	86 (91%)	6.84 (97.71%)	68 (91%)
Other statin	22 (21%)	19 (20%)	12 (11%)	7.00 (100.00%)	10 (100%)	5 (5%)	7.00 (100.00%)	6 (100%)	15 (14%)	6.89 (98.43%)	11 (79%)	5 (5%)	6.67 (95.29%)	2 (67%)
Perindopril	4 (4%)	6 (6%)	37 (35%)	7.00 (100.00%)	37 (95%)	37 (39%)	6.91 (98.71%)	33 (97%)	37 (35%)	6.92 (98.86%)	29 (85%)	37 (39%)	6.95 (99.29%)	30 (100%)
Bisoprolol	32 (30%)	25 (26%)	83 (79%)	7.00 (100.00%)	79 (98%)	74 (78%)	7.00 (100.00%)	66 (99%)	83 (87%)	6.88 (98.29%)	73 (96%)	74 (78%)	6.80 (97.14%)	62 (97%)
Amlodipine	25 (24%)	31 (33%)	89 (85%)	7.00 (100.00%)	86 (99%)	80 (84%)	7.00 (100.00%)	70 (99%)	90 (86%)	6.88 (98.29%)	77 (94%)	77 (81%)	6.84 (97.71%)	66 (96%)
ISMN	26 (25%)	23 (24%)	69 (66%)	6.93 (99.00%)	–	66 (69%)	7.00 (100.00%)	–	69 (66%)	6.96 (99.43%)	–	64 (67%)	6.97 (99.57%)	–
Nicorandil	3 (3%)	8 (8%)	49 (47%)	7.00 (100.00%)	46 (98%)	59 (62%)	6.94 (99.14%)	47 (96%)	49 (47%)	6.97 (99.57%)	45 (94%)	57 (60%)	6.97 (99.57%)	45 (92%)
Ivabradine	0	0	10 (10%)	7.00 (100.00%)	10 (100%)	7 (7%)	7.00 (100.00%)	6 (100%)	10 (10%)	6.67 (95.29%)	8 (100%)	7 (7%)	7.00 (100.00%)	7 (100%)
Ranolazine	0	0	6 (6%)	7.00 (100.00%)	7 (100%)	13 (14%)	7.00 (100.00%)	13 (100%)	6 (6%)	7.00 (100.00%)	6 (100%)	13 (14%)	6.89 (98.43%)	13 (100%)

Adherence to prescribed, protocol-directed cardiovascular medications as measured by self-report and HPLC MS/MS (detected). Self-reported adherence data are shown for each drug in response to the question "How many days in the preceding week did you take this medication?" A drug was "expected" if prescribed for that patient and a urinalysis sample was tested. A drug was marked "detected" if present in the urine on HPLC MS/MS. P-values are shown for the between groups difference in proportion of drug detected. ACEi, angiotensin-converting enzyme inhibitor; AP, anti-platelet drug, ARB, angiotensin II receptor blocker; BB, beta blocker; CCB, calcium channel blocker; PCI, percutaneous coronary intervention.

3.2 | Self-reported medication adherence

Self-reported adherence was >96% for all drugs in both treatment groups at both stages (Table 3).

3.3 | Urinary HPLC MS/MS

The proportion of expected drug detected was >90% for all first-choice, protocol-directed medicines at both stages. Conversely, percentage adherence below 80% was not demonstrated for any drug at pre-randomization and was only apparent in patients that were prescribed an alternative statin and who underwent urinary drug detection by HPLC MS/MS at follow-up: 11 of 14 (73%) patients in the PCI group and 2 of 3 (67%) patients in the placebo group.

4 | DISCUSSION

Adherence levels in our trial population were >90% for almost all drugs at both pre-randomization and follow-up, as measured by patient self-reporting of adherence and by urine HPLC MS/MS. There were no important between-group differences at pre-randomization or at follow-up and medication taking patterns did not change following treatment with PCI. There were no differences between self-reported and direct adherence measurement in our population, owing to near-perfect adherence levels by both measures.

Our results have shown that adherence levels in ORBITA were high in both groups at both stages, greater than is typically seen in clinical practice[22] and also greater than expected for a clinical trial population.[23] Adherence was higher than the widely-used 80% threshold[2] for good adherence throughout, high at pre-randomization and maintained through 6 weeks of follow-up, suggesting that it was not influenced by treatment assignment to PCI or to placebo. Furthermore, adherence was maintained for all protocol-directed drugs and classes of drug and patients were therefore not selectively adherent to one class of drug or another, nor was this influenced by treatment assignment. The OMT protocol and assessments of adherence within ORBITA were designed firstly to maximize the potential therapeutic impact of guideline directed anti-anginal drugs and secondly to identify any bias or chance variation in drug usage between the PCI and placebo procedure groups. These results emphatically corroborate the findings in the main ORBITA results paper, indicating that there was no difference in drug adherence between the two groups that might otherwise complicate interpretation of the ORBITA trial.

Within ORBITA, two research fellows had distinct roles, and both maintained close contact with patients throughout their involvement in respective phases of the study. Patients were committed to the study, received detailed study literature and had many opportunities to ask questions and learn more about their condition and available treatment options. This created an environment that fostered good doctor-patient communication and may have promoted good medication taking behavior, which could in part explain these very high adherence rates. Initially this took time and effort, but once patient contact had been made, implementation of the protocol was managed remotely via regular telephone clinics. This is a model that has the potential to be replicated in any clinical setting.[1,24] Our results show levels of adherence that are much higher than those reported for this patient population in clinical practice.[10–12] In order to bridge the gap between clinical trial conditions in ORBITA and those in clinical practice where optimization rates remain poor, clinicians treating patients with angina need to consider new approaches to enhance local services. In the UK, where cardiac rehabilitation for patients with stable angina is not universally available the delivery of such a service rests with general practitioners and cardiology clinics. We are pleased to note that stable angina as an indication for cardiac rehabilitation in the UK is the subject of a themed research call by the NIHR for further clinical research.[25] In the interim, medication optimization must remain a key focus for clinicians treating patients with stable angina, not least in the aftermath of the ISCHEMIA trial which reported that, with good medical therapy, there is no additional benefit of an upfront invasive strategy in stable CAD.[26]

Direct assessment of medication adherence is increasingly available and recognition of the importance of quantifying adherence in clinical trials is increasing. Non-adherence is often difficult to identify and subjective measures such as patient self-reporting and pharmacy prescription refill data can be error-prone.[27] Biochemical screening is direct, objective, specific and sensitive is increasingly used as the preferred method for detection of non-adherence in hypertension.[28] The method is available at low cost and samples can be sent unprepared. However, it requires significant technical expertise to develop and has some key limitations. The HPLC MS/MS measure directly captures adherence to each drug at the time of testing but nonetheless remains vulnerable to the "white coat adherence" phenomenon whereby patients ingest a single dose of drug just before testing to avoid detection of non-adherence.[29] Absence of a medication on a patient's test result implies that it was not ingested for 4–6 half-lives. This varies from 6–8 h for furosemide or 4–6 days for amlodipine.[30] Therefore while demonstration of absence of drug can be useful clinically, presence of drug in a tested sample does not imply persistence.

In the midst of the COVID-19 pandemic outpatient consultations have moved online at a rapid pace across a multitude of medical specialties including clinical cardiology.[31,32] Faced with necessary social distancing measures clinicians have rapidly adapted to carrying out clinical reviews using telehealth and for many patients this has become an expected way of accessing clinical care.[33] The telehealth approach implemented in ORBITA provides supportive evidence of how good medication optimization can be achieved by telephone. Overall, ORBITA has shown that implementation of a simple protocol of OMT is feasible and

practical with limited resources. The high adherence rates seen are evidence that the OMT protocol was successfully implemented and the study methodology therefore offers a model of how optimization can be achieved in clinical practice using a straightforward telehealth approach.

ORBITA STUDY INVESTIGATORS

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DISCLOSURE

Nothing to declare.

AUTHOR CONTRIBUTIONS

Dr. Thompson, Dr. Al-lamee, Prof. Thom, Dr. Davies and Prof. Francis were responsible for conception and design of the study. Dr Thompson and Dr. Al-lamee were responsible for data acquisition at the study coordinating centre. Dr. Patel and Dr. Gupta were responsible for laboratory analysis and data handling at the biochemistry laboratory and provided specialist chemical pathology advice. Dr. Dehbi was the study statistician. Dr. Foley carried out additional data checking and analysis. Dr. Thompson, Dr. Al-lamee and Prof. Thom carried out data interpretation and writing of the first draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

OPEN RESEARCH BADGE

This article has earned Open Data, Open Materials and Preregistered Research Design badges. Data, materials and the preregistered design and analysis plan are available in the article.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.[34]

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REFERENCES

1. Yach D. *Adherence to long-term therapies: evidence for action*. World Health Organisation. 2003. https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf;jsessionid=2BF96AB55A3F30957D1CC7618D951705?sequence=1.
2. Bansilal S, Castellano JM, Garrido E, et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J Am Coll Cardiol*. 2016;68(8):789-801.
3. Hirsh BJ, Smilowitz NR, Rosenson RS, Fuster V, Sperling LS. Utilization of and adherence to guideline-recommended lipid-lowering therapy after acute coronary syndrome: opportunities for improvement. *J Am Coll Cardiol*. 2015;66(2):184-192.
4. Leslie KH, McCowan C, Pell JP. Adherence to cardiovascular medication: a review of systematic reviews. *J Public Health*. 2018;41(1):e84-e94.
5. Burke LE, Ma J, Azar KMJ, et al. Current science on consumer use of mobile health for cardiovascular disease prevention. *Circulation*. 2015;132(12):1157-1213.
6. Gee ME, Bienek A, Campbell NRC, et al. Prevalence of, and barriers to, preventive lifestyle behaviors in hypertension (from a National Survey of Canadians with hypertension). *Am J Cardiol*. 2012;109(4):570-575.
7. Reynolds MW, Fredman L, Langenberg P, Magaziner J. Weight, weight change, mortality in a random sample of older community-dwelling women. *J Am Geriatr Soc*. 1999;47(12):1409-1414.
8. Al-Lamee R, Thompson D, Dehbi H-M, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31-40.
9. Robert AB. Fallout from the ORBITA trial – is angioplasty in a spin? *EuroIntervention*. 2017;13(11):1253-1254.
10. Borden WB, Redberg RF, Mushlin AI, Dai D, Kaltenbach LA, Spertus JA. Patterns and intensity of medical therapy in patients undergoing percutaneous coronary intervention. *JAMA*. 2011;305(18):1882-1889.
11. Garg P, Wijeysundera HC, Yun L, Cantor WJ, Ko DT. Practice patterns and trends in the use of medical therapy in patients undergoing percutaneous coronary intervention in Ontario. *J Am Heart Assoc*. 2014;3(4):e000882.
12. Elder DH, Pauriah M, Lang CC, et al. Is there a Failure to Optimize theRapy in anGina pEcToris (FORGET) study? *QJM*. 2010;103(5):305-310.
13. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;2013:346.
14. Katritsis DG, Ioannidis JPA. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease. *Circulation*. 2005;111(22):2906-2912.
15. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24(1):67-74.
16. Francis DP, Davies JE, Al-lamee R, et al. Protocol 15PRT/06897: objective randomised blinded investigation with optimal medical therapy of angioplasty in stable angina (ORBITA trial) - NCT02062593 [Protocol]. *Lancet*. 2016. http://www.thelancet.com/doi/story/10.1016/html.2016.10.12.4214
17. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2975–2981.
18. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP–ASIM guidelines for the management of patients with chronic stable

angina: executive summary and recommendations. *Circulation*. 1999;99(21):2829-2848.
19. Thom S, Poulter N, Field J, et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the umpire randomized clinical trial. *JAMA*. 2013;310(9):918-929.
20. Tomaszewski M, White C, Patel P, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart*. 2014;100(11):855-861.
21. Lane D, Alghamdi R, Muscat M, et al. 1424The diagnosis of non-adherence in hypertension using a urine biochemical screen is unaffected by drug pharmacokinetics. *Eur Heart J*. 2019;40(Supplement_1). https://academic.oup.com/eurheartj/article-abstract/40/Supplement_1/ehz748.0070/5597249?redirectedFrom=fulltext
22. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119(23):3028-3035.
23. Armstrong EJ, Chen DC, Westin GG, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc*. 2014;3(2):e000697.
24. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2014;11:19–25.
25. NIHR.HTA Funding Committee Public Minutes 19–20 May 2020. 2020. https://www.NIHR.ac.uk/documents/hta-funding-committee-public-minutes-19-20-may-2020/25078?pr=. Accessed 14/08/2020.
26. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382(15):1395-1407.
27. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-497.
28. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104.
29. Modi AC, Ingerski LM, Rausch JR, Glauser TA, Drotar D. White coat adherence over the first year of therapy in pediatric epilepsy. *J Pediatr*. 2012;161(4):695-699.e691.
30. Gupta P, Patel P, Horne R, Buchanan H, Williams B, Tomaszewski M. How to screen for non-adherence to antihypertensive therapy. *Curr Hypertens Rep*. 2016;18(12):89.
31. Eberly LA, Khatana SAM, Nathan AS, et al. Telemedicine outpatient cardiovascular care during the COVID-19 pandemic. *Circulation*. 2020;142(5):510-512.
32. Webster P. Virtual health care in the era of COVID-19. *Lancet*. 2020;395(10231):1180-1181.
33. Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. *N Engl J Med*. 2020;382(18):1679-1681.
34. Al-lamee R. Summary and contact. 2020. https://www.imperial.ac.uk/people/r.al-lamee13.

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