RAPID TREATMENT OF MODERATE TO SEVERE HYPERTENSION USING A NOVEL PROTOCOL IN A SINGLE CENTRE, BEFORE AND AFTER INTERVENTIONAL STUDY

(RUNNING TITLE: RAPID TREATMENT OF MODERATE-SEVERE HYPERTENSION)

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Abstract

Rapid treatment to target in hypertension may have beneficial effects on long-term outcomes. This has led to a new recommendation in the 2018 European hypertension guidelines for patients with Stage II/III hypertension to be treated to target within three months. However, whether it is feasible and safe to quickly manage treatment-naïve Stage II/III hypertension to target was unclear.

We examined this using a single centre before and after interventional study, treating newly-diagnosed, never-treated, Stage II/III hypertensive patients with a daytime average systolic ABP ≥150mmHg to target within 18 weeks. The proportion at office target BP at 18 weeks was determined, together with office and ambulatory BP change from baseline to after the intervention. The protocol was designed to maximise medication adherence, including a low threshold for treatment adaptation. Safety was evaluated through close monitoring of adverse events and protocol discontinuation.

55 participants were enrolled with 54 completing the protocol. 69 ±12.3% were at office target BP at their final visit, despite a high average starting BP of 175/103mmHg, as a consequence of significant reductions in both office and ambulatory BP. Of those at office target BP, 51% were above target on ambulatory measurement. Adherence testing demonstrated that 92% of participants were adherent to treatment at their final visit.

The accelerated management of treatment-naïve Stage II/III hypertension is feasible and safe to implement in routine practice and there is no evidence to suggest it causes harm. Further large-scale randomised studies of rapid, adaptive treatment, including a cost-effectiveness analysis, are required.

Summary Table

What is known about the topic?	• Retrospective data has indicated that rapidly achieving BP targets may benefit long-term cardiovascular outcomes. • Recent international consensus guidelines have recommended treatment to target within 3 months for moderate and severe hypertension.
What this study adds	• Achieving target BP in moderate and severe hypertension following only 18 weeks' treatment is feasible and safe. • Medication adherence within this study was higher than adherence reported in observational studies of hypertension treatment. • In those at target on office BP measurement, a high proportion of treated individuals were above target on ambulatory BP measurement.

Background

The nature and intensity of blood pressure (BP) lowering in high-risk hypertensive individuals (1), is a source of interest and debate. Achieving historical guideline BP targets has proven challenging, with only 63% of patients with treated hypertension in England achieving national targets (2). Following the recent American Heart Association/American College of Cardiology and European Society of Hypertension guidelines and recommendations for more stringent blood pressure control (3, 4), the challenge is now greater.

Protocol-directed therapy may improve the effectiveness of hypertension treatment by mitigating clinical inertia: the failure to initiate, intensify or change therapy despite clinical evidence and guidelines to support this. The magnitude of clinical inertia in hypertension treatment is unknown (5), however antihypertensive medications were not intensified as needed in 86.9% of clinical consultations in over 7000 patients in one US study (6).

The STICH-care (7) and the VIPER-BP studies (8), investigated the impact of protocol-directed therapy on hypertension treatment response. Both randomised controlled trials showed a higher proportion of grade 1 hypertension patients achieved target BP in the protocol-directed therapy arm. However, whether protocol-directed therapy is feasible and effective in treatment-naïve participants with moderate or severe hypertension is unknown.

Early BP control may confer better outcomes (9-12). Furthermore, control of grade II/III hypertension within 3 months of diagnosis has been recommended in the recent European guidelines for the treatment of hypertension (4). Rapid treatment to target may therefore offer an advantage, though the data remain surprisingly minimal on whether such an approach is safe, effective or well-tolerated.

We therefore devised a treatment protocol for patients with grade II/III hypertension constructed with the aim of participants reaching target BP within 18 weeks of their diagnosis. The protocol was designed to maximise drug tolerance, thereby optimising treatment adherence and BP control.

Methods

This was an open-label, single-centre, before and after interventional study design.

Participants were recruited from 22 primary care practices or from secondary care in the county of Devon, United Kingdom. Referred subjects were eligible for screening if they were aged 18-79 years, had an office systolic BP of ≥170mmHg and had never previously received antihypertensive treatment.

Exclusion criteria were: Glomerular Filtration Rate (GFR) <60ml/min/1.73m^2, previous renal artery intervention, haemoglobin <10g/dl, platelet count <100 x10^9/l, bleeding diathesis, pregnancy or breastfeeding, inability to provide informed consent, hypertension-related event (including stroke or acute kidney injury) within the preceding 3 months, or any condition, including hypertensive urgency, requiring more immediate BP lowering or tailored antihypertensive strategy at enrolment.

At screening, subjects underwent 24-hour ambulatory BP monitoring (ABPM) and were eligible for trial participation if this confirmed at least grade 2 hypertension with a daytime average systolic BP (DASBP) measurement ≥150mmHg as per current guidelines (13).

All participants gave informed consent and followed a treatment protocol using an antihypertensive medication pathway designed to maximise tolerance within an accelerated time frame, with appointments every 2-4 weeks over an 18-week period (Figure 1). At every visit they also received lifestyle advice in accordance with British Heart Foundation guidance.

Prior to treatment, all participants underwent 12-lead ECG, Epworth scoring and venous blood sampling for full blood count, electrolytes, liver function tests, HbA1c, fasting glucose

and fasting lipid profile. Serum was stored for subsequent more complete secondary hypertension screening in case patients proved resistant to treatment. Participants also consented to two overnight urine collections for microalbuminuria.

Patients under the age of 45 years underwent rigorous screening for secondary hypertension at the outset, whilst those over the age of 45 underwent screening if they proved to be drug resistant (as defined by a failure to respond to the first three antihypertensive agents in the protocol). This included cardiac magnetic resonance (CMR) imaging to exclude aortic coarctation, renal artery stenosis and adrenal adenomata, blood testing for thyroid function, calcium, renin, aldosterone and renal function and 24-hour urine testing for metanephrines and free cortisol levels.

If proven to be resistant to treatment, medication adherence was assessed by directly observing the participant ingesting each medication sequentially, with one hour between each medication. 24-hour ABPM was performed simultaneously and urine drug metabolite levels measured immediately prior to drug ingestion and at the same time on the following day. Urinary drug metabolite levels were also determined at the final visit.

Visit BP measurements (Omron M6) were made after 5 minutes seated with feet on the floor, in a quiet environment using an appropriately sized cuff. Following an initially discarded reading, the average of three subsequent readings was taken. The arm with the highest BP reading was determined at the initial screening visit and used for all subsequent BP measurements.

At all visits prior to or following medication changes, serum creatinine and electrolytes were determined to check for electrolyte disturbances or reduction in GFR. The protocol was followed as in Figure 1.

Medication intolerances

With a view to increasing adherence we aimed to minimise medication intolerance and prevent the association of the use of antihypertensive drugs with adverse effects. We employed a low threshold for changing or stopping medication. In the case of lightheadedness, moderate-severe symptoms triggered withdrawal of the most recently added drug, whereas mild symptoms were investigated with ABPM. If this demonstrated excessive control or dipping, drugs were also de-escalated.

Ankle swelling led to withdrawal or exchange of the calcium channel blocker; spironolactone was converted to eplerenone if gynaecomastia occurred and we maintained a low threshold for stopping medication for any other symptoms, including non-specific complaints such as lethargy or sleep disturbance. A creatinine increase of >30% from baseline led to discontinuation of the most recently introduced drug.

Study endpoints

The primary endpoint for the study was the proportion of participants achieving target office BP at 18 weeks.

The tolerability of the protocol was determined by assessing the proportion of participants who did not complete the protocol as outlined.

Key other secondary endpoints included the median number of antihypertensive medications prescribed at the end of the 18-week period, the proportion of participants diagnosed with secondary hypertension and the proportion with non-adherence to antihypertensive treatment

Sample size and statistical analysis

Using data from the Health Survey for England, it is reported that 63% of patients with known hypertension presently achieve consensus guidelines targets (2). In this study, we anticipated that a similar proportion could be achieved using our treatment programme in just 18 weeks.

Baseline and outcome data are presented as means (standard deviation) or medians (interquartile range) for continuous data depending on the normality of the data and counts (percentages with 95% confidence intervals) for categorical and binary variables. To facilitate meaningful statistical analysis of endpoints, including safety, we planned to recruit at least 50 participants, allowing for predicted participant dropout prior to the 18 weeks.

Parametric data were analysed using a paired t-test; non-parametric data were analysed using Wilcoxon's signed ranks test, proportions using a one-sample test of proportions and categorical data with McNemar's test. A two-sided *P* value threshold <0.05 was considered statistically significant. For multiple comparisons, a Bonferroni correction was applied.

Statistical analysis was performed using STATA v14.1 (StataCorp, College Station, Texas, USA).

Results

Recruitment took place from July 2015 to February 2017, during which time 170 potential participants were referred to the study. The basic referral criteria were not met in 27 subjects (referral office BP too low (9 patients); previously treated with antihypertensive medication (17); outside of age criteria (1)). Despite best efforts, 9 participants did not respond to contact from the study team, whilst 35 subjects declined a screening appointment after telephone consultation which described the study and what participation involved.

At screening, 11 declined study enrolment after face-to-face discussion of the protocol. A further 28 patients had DASBP measurement <150mmHg and therefore did not satisfy the BP inclusion criteria for the study. One patient was unable to undergo ABPM, 3 required immediate treatment for hypertensive urgency and 1 described an inability to tolerate tablet ingestion. The remaining 55 participants gave informed consent and were recruited to begin the treatment programme (Figure 2).

Of the 55 enrolled participants, 54 completed the treatment programme as outlined in Figure 1, with 1 patient withdrawing consent after 14 weeks of treatment. The following results therefore pertain to the remaining group of 54 participants. The mean age of this group was 59 ± 11 years and 22 (40%) were female. Obstructive sleep apnoea was excluded in all participants: median Epworth Score = 5 (interquartile range: 3-8).

The characteristics of enrolled patients before and after treatment are given in Table 1.

Primary endpoint and BP reduction

Despite the high average screening office BP for the cohort of 175/103mmHg, 69% ± 12.3% (n=37) achieved target at 18 weeks. Marked reductions in office BP were seen in both systolic and diastolic readings (Figure 3A-B), with mean office BP being 175 ± 16 / 103 ± 11mmHg when taken by the study team at enrolment, reducing to 132 ± 12 / 80 ± 9mmHg at week 18 ($p<0.0001$). This was remarkably well-tolerated by participants.

The protocol targeted office BP; however, ambulatory BP also significantly improved during the study period (Figure 3C-D) with 44 ±13.2% participants at the target of <135/85mmHg on ABPM at week 18. Mean daytime average ambulatory BP reduced from 163 ± 11 / 93 ± 9mmHg at study enrolment to 135 ± 10 / 78 ± 7mmHg at week 18 ($p<0.0001$).

Overall, of the 37 patients who achieved target on office blood pressure at 18 weeks, 19 (51 ±16.1%) participants were not at target BP on ABPM, defined as ≥135/85mmHg (indicating masked hypertension). Furthermore, 6 (11 ±8.4%) of the total number of 54 participants were not at office target at week 18 but were at target BP on ABPM (indicating white coat hypertension).

Safety and tolerability

The protocol was well-tolerated, with only one participant withdrawing during the study. Medication intolerances requiring drug discontinuation are summarised in Table 2.

Creatinine increased by >30% after the introduction of candesartan in 5 participants and in 1 participant after the addition of indapamide. In each case, the newly-introduced

medication was withdrawn and renal function returned to normal within 2 weeks. None of these patients had evidence of renovascular disease on CMR.

There was no significant increase in either HbA1c or fasting glucose at week 18 (Table 1). There were no episodes of syncope in participants throughout the study period.

Non-adherence

Once patients were taking 3 antihypertensive medications, if their office BP remained ≥140/90mmHg, adherence testing was performed with directly observed therapy (DOT) (median point of assessment: 16 weeks). In the 11 participants proven to be resistant to treatment, urinary drug levels before and after DOT showed that all were adherent to treatment immediately prior to this appointment.

In addition, urine drug testing was performed at the final (18 week) visit for 51 of the 54 patients (94 ±6.3%), as urine samples were not stored for three patients. Due to the drug not being measured by the urinary assay, we were unable to confirm adherence for lercanidipine in the three patients receiving this drug. However, it is noteworthy that these patients were adherent to all their other antihypertensive medications. In the remaining 48 patients we demonstrated non-adherence for 4 patients to one of their medications (whilst they were adherent to their other prescribed antihypertensive drugs); one to candesartan, one to bendroflumethiazide and two to doxazosin. Thus, in those 48 patients in whom we were able to fully assess adherence, 44 (92 ±7.7%) were adherent to all of their antihypertensive therapy.

Response to lifestyle advice

Intensive lifestyle advice and behavioural modification support was offered at every appointment, with British Heart Foundation literature also provided at enrolment for all participants. Despite this, there was no significant change in BMI, body fat percentage, arm circumference, smoking status, patient-reported alcohol intake or weekly exercise at week 18 compared with enrolment (Table 1).

Secondary hypertension

Seven participants were aged under 45 years at enrolment and therefore underwent immediate extended testing to exclude secondary hypertension - all testing was negative. A further 16 participants underwent extended secondary hypertension screening after the third drug introduction step in the protocol (as previously defined) - two of these were found to have biochemical profiles consistent with Conn's syndrome. Aside from this, following blood, urine and CMR assessments, no other diagnoses of secondary hypertension were made, suggesting a 3.7 ±5.0% prevalence of secondary hypertension in the entire cohort.

Number of antihypertensive medications prescribed

A mean of 2.7 medications were prescribed per participant at their final visit. Of the 23 (43 ±13.2%) patients prescribed three medications at their final visit, 6 (26 ±9.7%) were above

267 office target BP. A further 8 (15 ±7.2%) were prescribed more than three medications at
268 their final visit indicating that, of all participants completing the study, 14 (26 ±11.7%) could
269 be described as being resistant to antihypertensive treatment according to the standard
270 office BP definition (above target on ≥3 antihypertensive medications at optimal doses and
271 of different classes (including a diuretic) or at target on 4 or more antihypertensive
272 medications at optimal doses (14)). None of these reached the a priori protocol threshold
273 for considering renal denervation.

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Discussion

Our study demonstrates for the first time that rapid management of treatment-naïve moderate-severe hypertension via an 18-week, dedicated protocol is feasible and there is no evidence of harm using this approach. Overall, 69 ±12.3% of participants achieved an office BP target of <140/90mmHg at week 18, a comparable figure to data from the Health Survey for England, which reported a 63% control rate to <140/90mmHg for patients with treated hypertension in 2011 (2). This control rate also compares to contemporaneous data published concerning hypertension treatment in London, which suggests the "rule of halves" for BP control is still relevant today, albeit in an urban, mixed ethnicity population (15). However, of those at target on office BP in the present study, 51 ±16.1% were found not to be at target on ABPM as defined as daytime average BP <135/85 mmHg (16).

By nature of the selection criteria for the study, the cohort exhibited a higher starting office BP than that of a normal hypertensive population. Screening office BP for this cohort averaged 175/103mmHg, compared to that of 164/95mmHg in the ASCOT BPLA study (17).

Using an average of 2.7 medications per patient, mean ± standard deviation office systolic BP reduction was 43 ± 15mmHg and mean office diastolic BP reduction was 23 ± 9mmHg over 18 weeks. This compares favourably with a mean 18mmHg office systolic BP reduction after one year's treatment with an average of 2.8 medications in the SPRINT trial intensive treatment group (1). These substantial and rapid office BP reductions in our study were well-tolerated.

We demonstrated adherence in 44 out of 48 patients in whom it was possible to assess this at the final visit. This excellent adherence may have been due to, at least in part, the design

and delivery of the protocol, though the design of the study without a control arm means that this conclusion cannot be definitively drawn. Alternatively, this cohort with treatment-naïve grade II/III hypertension may have been more receptive to pharmacological therapy than comparable cohorts, which is plausible given the early onset of aggressive treatment following diagnosis.

Ambulatory BP response

The prevalence of masked hypertension was ~35% in our sample following antihypertensive treatment, as defined by office BP <140/90mmHg and daytime ABPM ≥135/85mmHg. This finding is similar to previous cross-sectional study of over 12,000 patients, determining a 30.5% prevalence of masked hypertension in non-diabetic subjects on antihypertensive treatment (18).

In this study we targeted office BP, as per international guidelines. However, despite achieving this target in 69% of patients, more than half of those at office target were above target on ABPM. This raises the question of whether successful completion of a protocol-directed antihypertensive treatment programme should be decided by office BP alone. Residual elevation of ambulatory BP is associated with raised cardiovascular risk and could partly explained the phenomenon of “residual risk” described in treated high-risk individuals (19).

Safety and tolerability

The impact of protocol-directed therapy in hypertension treatment has been investigated by two randomised controlled trials. Firstly, a cluster-randomised controlled trial of 2104 patients conducted in primary care in Canada studied the effect of implementing a simplified stepped-care algorithm for BP treatment (the STITCH-care protocol), with control practices continuing with usual care. A majority of patients had only mild hypertension and treatment success was determined after 6 months. The intervention practices were found to achieve target office BP in 64.7% participants versus 52.7% in control practices (7).

In the VIPER-BP study, 1562 patients in Australia with uncontrolled hypertension were randomised to protocol-directed treatment over 26 weeks versus usual care (8). Over 60% of enrolled patients were already treated for hypertension and the mean entry BP indicated that most had mild hypertension. Subsequently, 36.2% patients achieved office target BP after 26 weeks' treatment in the intervention group, versus 27.4% in the control group, a difference which reached statistical significance. However this was at the expense of high rates of treatment side effects and participant withdrawals (20).

The mean office BP of participants at randomisation in the VIPER-BP study was 149/87mmHg and in those receiving the intervention in the STITCH-Care study the mean entry office BP was 155/88mmHg. In our study, the mean office BP taken at the time of enrolment by the study team was 175/103mmHg. As such, our study demonstrates that an accelerated protocol-directed approach is feasible in those with moderate-severe hypertension, building on the previous data from STITCH-Care and VIPER-BP demonstrating efficacy in individuals predominantly with grade 1 hypertension. Given that both previous studies measured their primary outcome after 6 months, our 18-week protocol proves that a more rapid treatment protocol is feasible. Given the recent ESC guidelines recommending BP control within 3 months for patients with grade 2 and grade 3 hypertension(4), the

difference in timeframe for the study protocols is certainly relevant. Moreover, we demonstrate that this model of care is applicable to the UK healthcare system, with STITCH-Care taking place in Canada and VIPER-BP in Australia. The limiting factor of our study in comparison with STITCH-Care and VIPER-BP is the absence of a control group to prove efficacy. This could be addressed in the future by a randomised double blind control trial now that our study has shown feasibility, safety and reductions in BP compared to before the intervention.

Therefore, the present study demonstrates, in newly-diagnosed grade II/III hypertensive patients, that rapid reduction of BP over 18 weeks is feasible. Achieving target rapidly could confer benefits above and beyond BP control as demonstrated in a retrospective analysis of the VALUE study (21) which showed that patients who reach target BP after 6 months' treatment have a legacy benefit of improved cardiovascular outcomes up to 6 years later (11). Furthermore, an initial response to antihypertensive treatment (within 1 month) also conferred a prognostic advantage in VALUE.

A similar effect has been noted in retrospective analysis of the Syst-Eur trial (22), during which a control group were left untreated for hypertension for 6 months, which appears to have conferred an increase in cardiovascular event rate in this group during open-label follow-up for a median period of 6 years (12).

Although these retrospective analyses can be criticised for employing post-hoc interpretations of studies designed for another purpose, potentially biasing the results, this flaw has been addressed by two subsequent studies specifically designed to explore the effect of delayed treatment on cardiovascular outcomes. Firstly, it has been shown that patients who suffer a cardiac event are consistently less likely to be at BP target, as determined by retrospective analysis of over 3000 sets of primary care electronic notes (9).

Furthermore, a delay in intensifying treatment in response to above-target BP measurements confers a significantly increased risk of subsequent cardiovascular events or all-cause mortality, even when this delay is only 18 weeks, as shown by retrospective analysis of over 88,000 primary care case notes (10).

Given the substantial BP reductions seen here over an 18-week period, it is notable that the protocol was remarkably well-tolerated by participants. This was a highly selected group. Nevertheless, only one participant withdrew from study participation (1.9%), which compares favourably with the dropout rate seen in similar studies of BP treatment protocols, such as the VIPER-BP study (8) (5.0% dropout after randomisation in intervention group) and the STITCH-care protocol (7) (2.9% dropout rate in intervention group). Our protocol involved more frequent visits than either the VIPER-BP study or STITCH-Care protocol. Given the low dropout out rates from our study in comparison, we conclude that the higher frequency of visits was acceptable to our participants, though of course other participants may have declined to join the study due to the number of visits involved.

The study protocol was designed to minimise drug side effects. By intervening in patients at the earliest possible time-point in their hypertensive disease process, before aortic stiffness and clinically-important BP variability become more prevalent, we theorised that tolerability to treatment may be improved. This theory requires testing in a larger trial.

Whilst 10 patients underwent discontinuation of medications due to lightheadedness, no syncopal events were reported throughout the study period. This number reflects the low threshold for changing medication within the study. The study team were instructed to ask directly at each appointment for these symptoms and to switch medications accordingly. This approach aimed to prevent the association of antihypertensive medication with side effects, thereby improving adherence to treatment.

Despite the rapid BP reductions observed, any episodes of altered renal function resolved following medication de-escalation. There was also no change in glucose handling using the rapid treatment protocol in our study.

Non-adherence

In the present study, we were able to demonstrate adherence in 44 out of 48 subjects (92 ±7.7%) on urine drug testing using samples which were taken on arrival for their week 18 visit. The patients were not pre-warned that they would be undergoing urinary metabolite testing before the sample was obtained.

Our adherence rates are outstanding when compared with a prior study of patients with uncontrolled hypertension attending a specialist clinic who were assessed by simultaneous DOT and ABPM. This process demonstrated a 50% non-adherence rate (23), in keeping with retrospective observational studies of self-reported adherence in hypertensive patients, which have found an approximately 40% rate of medication discontinuation (24, 25).

Other studies have used liquid chromatography urine analysis to determine the presence of antihypertensive agents and their metabolites, as also employed in the present study. This technique has previously indicated a non-adherence rate of 53% in patients with resistant hypertension seen in a specialist clinic (26). A further study used the same method to determine an adherence rate of 75% in patients referred to a secondary care hypertension clinic, though the sample was a heterogeneous group of participants, including new referrals from primary care together with some patients with resistant hypertension under consideration for renal denervation (27).

Our excellent adherence rates may be due to the short duration of our study in comparison to the long durations of antihypertensive treatment in the observational studies. Furthermore, through participation in an interventional study, including frequent follow-up with members of the study team, we may have substantially increased adherence in our sample. The potential selection bias of highly-motivated participants willing to participate in a study of antihypertensive treatment will also have affected adherence, as will the selection bias inherent in referral to a specialist hypertension clinic in the comparator studies described.

Despite these caveats, the finding of 92% antihypertensive medication adherence on urinary testing in the present study is an interesting finding in a study where the protocol was designed to minimise drug side effects. The experience of side effects with anti-hypertensive medications is a factor known to increase non-adherence.

Furthermore, we theorised that tolerability would be improved by treating patients at the first possible point in the disease process (within days of first diagnosis of hypertension), before advanced hypertensive vascular disease can develop.

Whether the excellent adherence rate described is due to the protocol or other factors cannot be determined given the limitations of the study design and lack of control group, though this possibility could be explored in a future randomised controlled study.

Lifestyle measures

The present study explored the short-term impact of lifestyle measures and patient education, using methods which were designed to mimic usual care but were delivered

more frequently. Despite being delivered 2-4 weekly over 18 weeks, our lifestyle intervention had no impact on participant anthropometry, smoking status, alcohol intake or exercise habits. This is despite the recruitment of a sample of patients likely to be highly motivated, having agreed to participation in an intensive research programme for treatment of hypertension and in whom 92% adherence to medication was demonstrated.

Secondary hypertension

Through systematic investigation of all patients with resistant hypertension and those aged under 45 years at enrolment, we determined a 3.7 ±5.0% prevalence of secondary hypertension in our cohort overall.

This finding is in keeping with previous studies (28-31), though in our study, patients with significantly impaired renal function were excluded.

Study limitations

The before and after study design limits the conclusions in terms of attributing the remarkable control rates of moderate-severe hypertension to the protocol itself rather than other factors acting upon the single treatment group. Nevertheless, the data presented affirm that a rapid, protocol-directed treatment approach for the treatment of moderate-severe hypertension is feasible and could be implemented in routine practice or within a larger multi-centre randomised controlled study in order to prove effectiveness over standard care.

The protocol presented is intensive, including a large number of visits within a short period of time. The cost-effectiveness of such a strategy can therefore be questioned, though it is argued that the study aims to perform the usual number of visits for which patients with newly-diagnosed hypertension would expect to receive, though just in a shorter period of time. By using protocol-directed treatment, it is hoped that consultations within the protocol could be provided by allied healthcare professionals, rather than primary care physicians, providing further cost savings. Such a strategy could also potentially enhance the effectiveness of the treatment(32). Furthermore, by providing a putative benefit in terms of cardiovascular outcomes, it is possible that additional cost savings could be made. In view of these unknown factors, it would be reasonable to suggest that a cost-effectiveness analysis should be performed alongside a future randomised controlled trial of this treatment protocol before it can be recommended as the standard of care in the UK.

The single centre design of the study also limits the generalisation of its conclusions to the wider population, though we hope that this could be addressed by the proposed future study.

Conclusion

This study shows for the first time that the rapid treatment of moderate-severe hypertension using a protocol-directed regimen, designed to minimise drug side effects and improve tolerability, can be implemented in usual care with no evidence of harm. BP reductions occurring as a consequence of this treatment were remarkably well-tolerated, with urine drug testing demonstrating 92% adherence to medication within the study.

Earlier BP control in the newly diagnosed grade II/III hypertensive population could plausibly deliver gains in terms of medication adherence, BP control and even offer the potential for improved cardiovascular outcomes. Further randomised large scale studies of this concept are required.

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Conflicts of Interest / Disclosures

The authors have no conflicts of interest to declare.

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611 # Table 1: Participant characteristics

Variable	Before treatment	After treatment	P value
Office systolic BP (mmHg)	175 ± 16	132 ± 12	<0.0001
Office systolic BP <140mmHg (n;%)	0	41 (76 ±11.4)	
Office diastolic BP (mmHg)	103 ± 11	80 ± 9	<0.0001
Office diastolic BP <90mmHg (n;%)	6 (11 ±8.4)	46 (85 ±9.5)	
Office BP <140/90mmHg (n;%)	0	37 (69 ±12.3)	
Daytime average systolic BP (mmHg)	163 ± 11	135 ± 10	<0.0001
Daytime average systolic BP <135mmHg (n;%)	0	26 (48 ±13.3)	
Daytime average diastolic BP (mmHg)	93 ± 9	78 ± 7	<0.0001
Daytime average diastolic BP <85mmHg (n;%)	14 (26 ±11.7)	43 (80 ±10.7)	
Daytime average BP <135/85mmHg (n;%)	0	24 (44 ±13.2)	
Heart rate (bpm)	70 ± 11	66 ± 9	<0.006*
Inter-arm systolic BP difference ≥10mmHg (n;%)	6 (11 ±8.4)	4 (7 ±6.8)	0.35**
BMI (kg/m^2)	29.9 ± 5.6	29.9 ± 5.4	0.93
Waist circumference (cm)	103 ± 13	103 ± 13	0.99
% body fat	34.5 ± 8.5	34.4 ± 8.2	0.80
Current smoker (n)	6 (11 ±8.4%)	6 (11 ±8.4%)	1.00**
Alcohol (units/week)	7 (1-15)	4 (1-10)	0.59*

Weekly exercise (hours)	4 (1-7)	5 (2-8)	0.96
Fasting total cholesterol (mmol/L)	5.5 ± 1.1	5.5 ± 1.2	0.54
Fasting glucose (mmol/L)	5.5 ± 0.6	5.5 ± 0.6	0.93
HbA1c (mmol/mol)	38 ± 3.4	38 ± 3.7	0.60
Serum sodium (mmol/L)	140 ± 2.0	138 ± 2.2	<0.0001
Serum potassium (mmol/L)	4.6 ± 0.4	4.4 ± 0.5	0.004
Creatinine (μmol/L)	75 ± 13	77 ± 14	0.09
Urine albumin/creatinine ratio	0.825 (0.5-2.7)	0.7 (0.5-1.4)	0.0094
Urine albumin excretion rate (mg/day)	8.5 (5-18.5)	7 (5-16)	0.017
Angiotensin receptor blocker(n;%)	0	46 (85 ±9.5%)	n/a
Calcium channel blocker(n;%)	0	53 (98 ±3.7%)	n/a
Thiazide diuretic(n;%)	0	31 (57 ±13.2%)	n/a
Aldosterone antagonist(n;%)	0	11 (20 ±10.7%)	n/a
α-blocker(n;%)	0	3 (6 ±6.3%)	n/a
β-blocker(n;%)	0	3 (6 ±6.3%)	n/a

Characteristics of 54 participants with moderate-severe hypertension before and after 18 weeks' antihypertensive treatment with P values determined between groups using a paired t test unless otherwise indicated (Expressed as mean ± standard deviation, proportion ± 95% confidence interval or median and interquartile range; *Wilcoxon's signed ranks test; **one-sample test of proportions). With Bonferroni correction, p<0.0017 considered significant.

Table 2: Intolerance of medication during treatment

	Candesartan (n=54)	Amlodipine (n=54)	Indapamide (n=35)	BFZ (n=2)	Spironolactone (n=14)	Doxazosin (n=4)
Light-headedness	1 (2)	0	5 (14)	1 (50)	2 (14)	1 (25)
Lethargy	2 (4)	1 (2)	0	0	2 (14)	0
Ankle swelling	0	3 (6)	0	0	0	0
Cr increase ≥30%	5 (9)	0	1 (3)	0	0	0
Total intolerant	8 (15)	4 (7)	6 (17)	1 (50)	4 (29)	1 (25)

Intolerance of medication used in a rapid treatment protocol in 54 newly-diagnosed treatment-naive patients with moderate-severe hypertension (Number(%); BFZ: bendroflumethiazide; Cr: creatinine; no intolerance to either bisoprolol or lercanidipine)

Figure Legends

Figure 1: Treatment protocol used to initiate and intensify antihypertensive therapy in treatment-naïve patients with moderate-severe hypertension

Figure 2: Flowchart showing study recruitment of treatment-naïve subjects with moderate-severe hypertension, aged 18-80 years and subsequently fulfilling enrolment criteria at screening

Figure 3: BP reduction for 54 participants with never treated moderate-severe hypertension before and after completing an 18-week treatment protocol. (A Office systolic BP; B Office diastolic BP; C Daytime average systolic BP; D Daytime average diastolic BP)