Management of Hypertensive Patients With Multiple Drug Intolerances: A Single-Center Experience of a Novel Treatment Algorithm

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Multiple drug intolerance to antihypertensive medications (MDI-HTN) is an overlooked cause of nonadherence. In this study, 55 patients with MDI-HTN were managed with a novel treatment algorithm utilizing sequentially initiated monotherapies or combinations of maximally tolerated doses of fractional tablet doses, liquid formulations, transdermal preparations, and off-label tablet medications. A total of 10% of referred patients had MDI-HTN, resulting in insufficient pharmacotherapy and baseline office blood pressure (OBP) of 178±24/94±15 mm Hg. At baseline, patients were intolerant to 7.6±3.6 antihypertensives; they were receiving 1.4±1.1 medications. After 6 months on the novel MDI-HTN treatment algorithm, both OBP and home blood pressure (HBP) were significantly reduced, with patients receiving 2.0±1.2 medications. At 12 months, OBP was reduced from baseline by 17±5/9±3 mm Hg ($P<.01$, $P<.05$) and HBP was reduced by 11±5/12±3 mm Hg ($P<.01$ for both) while patients were receiving 1.9±1.1 medications. Application of a stratified medicine approach allowed patients to tolerate increased numbers of medications and achieved significant long-term lowering of blood pressure. *J Clin Hypertens (Greenwich).* 2016;18:129–138. © 2015 The Authors. *The Journal of Clinical Hypertension* published by Wiley Periodicals, Inc.

Hypertension is a major risk factor for cardiovascular morbidity and mortality worldwide,[1] for which management is based on two principal, complementary approaches—lifestyle modification and lifelong adherence to antihypertensive medication.[2–4] Despite the availability of numerous medication classes that lower blood pressure (BP), hypertension is adequately controlled to guideline-recommended levels in <50% of treated patients.[5] Numerous factors may contribute to suboptimally controlled BP levels, including failure to adopt proven lifestyle interventions,[6] secondary forms of hypertension,[7] treatment-refractory hypertension,[8] and physician inertia.[9]

A further patient-related factor that is increasingly recognized as a contributory cause of failure to attain BP control is imperfect (or non-) adherence to prescribed medication;[10,11] only 50% of hypertensive patients persist with antihypertensive medications after 12 months.[12,13] Techniques to identify such patients with directly observed therapy followed by ambulatory BP (ABP)[14] or with analytical drug (or drug metabolite) measurement in both urine and plasma have recently demonstrated high levels of partial (or total) *covert* nonadherence to prescribed medications in difficult-to-treat hypertensive patients.[15,16] Causes of imperfect adherence can be patient related (lack of understanding of cardiovascular [CV] disease risk factors or reluctance to take lifelong medication), physician related (insufficient time/resources, incorrect assumption of patient education about CV disease), or medication related (high dosing frequency, polypharmacy, adverse drug reactions [ADRs]).[17,18] Many of these issues can be targeted by combining personalized, intensified, patient-focused programs and simplified dosing regimens, including fixed-dose combinations.[19,20] However, an overlooked cause of poor adherence, that is not amenable to the interventions listed above, is multiple drug intolerances (*overt* nonadherence), which prevents sufficient pharmacotherapy to achieve BP control.

Achieving optimal adherence in patients with hypertension is challenging. Patients are generally asymptomatic and therefore unlikely to choose to tolerate medications that make them feel in any way worse than their baseline state, especially as common ADRs related to antihypertensive therapy include sexual and cognitive dysfunction. Furthermore, the taking of medication for primary prevention only serves to reduce a frequently distant risk of future events thereby removing the positive reinforcement aspect of disease-recurrence avoidance. Regardless of the cause, if ADRs are distressing and incapacitating enough to significantly affect quality of life and warrant discontinuation of therapy, then they pose a particular therapeutic challenge in primary and specialist care. The patients inevitably are difficult to treat with very few treatment

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options, as there is no published evidence of an effective treatment stratagem despite being at high CV risk as a result of uncontrolled BP.

The term *multiple drug intolerance* (MDI) syndrome has been used to describe patients who express ADRs to three or more drugs of any class without a known immunological mechanism.[21] There has been little interest in such patients to date, evidenced by the lack of acknowledgement, description, or definition of this group in existing international guidelines.[2–4] Furthermore, since the publication of recent reports on device-based treatments for resistant hypertension,[22] we have seen increasing referrals of patients with uncontrolled BP and multiple drug intolerances to antihypertensive medication (MDI-HTN) to our clinic as both referring physicians and patients now contemplate nonpharmacologic approaches to difficult-to-treat hypertension. However, these patients have been excluded from existing clinical trials of device-based therapies as they most commonly fail to tolerate more than three antihypertensive medications required for a traditional definition of resistant hypertension,[2–4] which is a core inclusion criterion of existing device-based hypertension trials[22–24] backed up by recent international consensus guidelines.[25.]

We developed a medication-based, novel treatment algorithm specifically for patients with MDI-HTN that was initiated as part of routine care in our center. In this study, we sought to determine the impact of our algorithm in a cohort of MDI-HTN patients who were referred for expert management or consideration of entry into clinical trials of device-based interventions.

METHODS

We conducted a retrospective analysis of electronic and paper records for patients referred to the Barts BP Centre of Excellence for a 24-month period from July 2012 onwards. All patient-identifiable fields were removed before analysis. This analysis was conducted as part of a clinical effectiveness/quality improvement project and received approval from the institutional review board.

Patients

Patients were defined as having MDI-HTN if they had a documented history (at referral or new patient visit) of intolerance to at least three unrelated classes of antihypertensive medications (that resulted in not being prescribed that particular medication any further) with the result that patients were unable to take a conventional guideline-based regimen of antihypertensives[4] and therefore did not meet the conventional criteria of resistant hypertension.[2–4] Intolerances were included irrespective of subtype (ie, if there were type 1 hypersensitivity reactions, pharmacodynamically predictable or pharmacodynamically unpredictable).

Patients were included for analysis if they had:

- MDI-HTN.
- Confirmed uncontrolled BP by 24-hour ABP monitoring (daytime mean, systolic BP [SBP] >135 mm Hg and/or diastolic BP [DBP] >85 mm Hg).[4]
- A minimum of three clinic visits (new patient +2 follow-up) with >6 months of follow-up.
- Complete medication/dose/formulation/posology information for each visit.
- Complete clinic BP information for each visit.
- Existing use of home BP monitoring at referral, and continued use for intervisit periods.

Exclusion criteria included hypertension <1 year duration since diagnosis, and secondary cause of hypertension.

Data Extraction

Once patients with MDI-HTN were identified, data from electronic health records were extracted. Any missing data were searched for manually in paper health records, including:

- Demographics and anthropometric data.
- Reasons and mode for referral.
- Health-related lifestyle issues.
- Medical diagnoses, hypertensive target organ damage (TOD), BP, and biochemical indices.
- Current (and previous) antihypertensive and other drugs (medication/dose/formulation/posology).

Medication schedules between patients were compared by percentage of maximal licensed (or recommended) dose (MLD) for hypertension as listed in pharmacopoeia such as the British National Formulary.[26] For medications such as spironolactone, that is recommended for use in hypertension[4] but is not licensed, and other medications that did not have a specific license for hypertension, such as tadalafil, we decided on an appropriate maximum dose that we would not exceed in usual clinical practice (Table I). For each patient, the sum of the percentage of the MLD for each medicine gave a total whole medicine equivalent (WME).

For example, a patient taking bendroflumethiazide 2.5 mg daily (MLD for hypertension 2.5 mg daily, therefore 1.0 WME) and amlodipine 5 mg daily (MLD 10 mg daily, therefore 0.5 WME) has a total of 1.5 WME on two medications.

In contrast, a patient taking losartan 25 mg daily (MLD 100 mg daily, therefore 0.25 WME) and bisoprolol 5 mg (MLD 20 mg daily, therefore 0.25 WME) has a total of 0.5 WME on two medications.

For comparison of baseline demographics and characteristics, we randomly chose 30 patients of the remaining patients referred to Barts BP Centre of Excellence and analyzed their records in a similar fashion (reference cohort).

BP Measurements

Clinic BP. Clinic BP was recorded according to established guidelines[4] using a validated monitor for clinical use (Omron 705IT, Omron Corporation, Tokyo, Japan) and an appropriately sized cuff. The lowest of at least three readings was used as clinic BP.[4]

Home BP. Patients were instructed to conduct home BP monitoring for between 4 and 7 days, immediately prior

TABLE I. Sample of Available Formulations of Most Commonly Used Antihypertensive Medications From Recommended and Other Classes With Minimum Tablet Size (Below Which Was Considered Fractional Tablet Dosing) and Maximum Licensed or Recommended Dose[26]

Medication Class/Name	Minimum Tablet Weight	Maximum Licensed (Recommended) Daily Dose	Alternative Formulation (Strength)
ACE inhibitor/ARB			
Ramipril	1.25 mg	10 mg	Liquid (2.5 mg/mL)
Lisinopril	2.5 mg	80 mg	
Candesartan	2 mg	32 mg	
Losartan	25 mg	100 mg	Liquid (12.5 mg/mL)
CCB			
Amlodipine	5 mg	10 mg	
Felodipine	2.5 mg	20 mg	
Nifedipine[a]	20 mg MR	90 mg MR	Liquid (20 mg/mL)
Verapamil	40 mg (120 mg MR)	480 mg (480 mg MR)	Liquid (40 mg/5 mL)
Diuretics			
Indapamide	2.5 mg (1.5 mg MR)	2.5 mg (1.5 mg MR)	
Bendroflumethiazide	2.5 mg	2.5 mg	
Furosemide	20 mg	80 mg	Liquid (20 mg/5 mL)
Torasemide	2.5 mg	5 mg	
MRA			
Spironolactone[b,c]	25 mg	100 mg[d]	Liquid 10 mg/5 mL
Eplerenone[b]	25 mg	400 mg[d]	
β-Blocker			
Atenolol	25 mg	50 mg	Liquid (25 mg/5 mL)
Bisoprolol	1.25 mg	20 mg	
α-Blocker			
Doxasozin	1 mg	16 mg	
Terasozin	2 mg	20 mg	
Centrally acting			
Clonidine	0.025 mg	1.2 mg	Transdermal 0.1–0.3 mg/d
Moxonidine	0.2 mg	0.6 mg	
Vasodilators			
Hydralazine	25 mg	100 mg	
Isosorbide mononitrate[b]	10 mg (25 mg MR)	120 mg (120 mg MR)[d]	
Glyceryl trinitrate[b]	n/a	10 mg[d]	Transdermal 5–15 mg/d
Tadalafil[b]	2.5 mg	10 mg[d]	

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MR, modified-release; MRA, mineralocorticoid antagonist. [a]Nifedipine (plain) is only available in the United Kingdom as capsules and therefore cannot reliably be fractionally split. For the purposes of use of nifedipine MR (once-daily), doses are quoted for Adalat LA (as different versions of MR preparations may not have the same clinical effect). [b]Unlicensed indication. [c]Spironolactone is unlicensed although recommended by United Kingdom guidelines 4. [d]Maximum recommended dose established as the dose that our hypertension specialists would not increase above.

to clinic visits, with two readings in sequence in the morning (1 hour premedication) and evening (at least 1 hour on either side of evening meal and medication). The first day's readings were discarded and all other readings were averaged to provide home BP as per UK national guidelines.[4] Patients were given instructions to use a validated monitor for home use and an appropriately sized cuff.

Ambulatory BP. Daytime ABP was recorded using validated monitors according to established guidelines.[4]

Biochemistry

Blood samples were sent to the Department of Clinical Biochemistry at Barts Health NHS Trust as part of routine monitoring, including serum creatinine (sCr), estimated glomerular filtration rate (eGFR; by Chronic Kidney Disease Epidemiology Collaboration equation estimation), and total cholesterol/high-density lipoprotein cholesterol ratio.

Echocardiography

Standard transthoracic echocardiographic views were routinely obtained to determine interventricular septal width (in diastole) as a measure of left ventricular hypertrophy (upper limit of normal 12 mm).

MDI-HTN Algorithm

Our novel, hierarchical treatment algorithm was based on four strata (Figure 1):

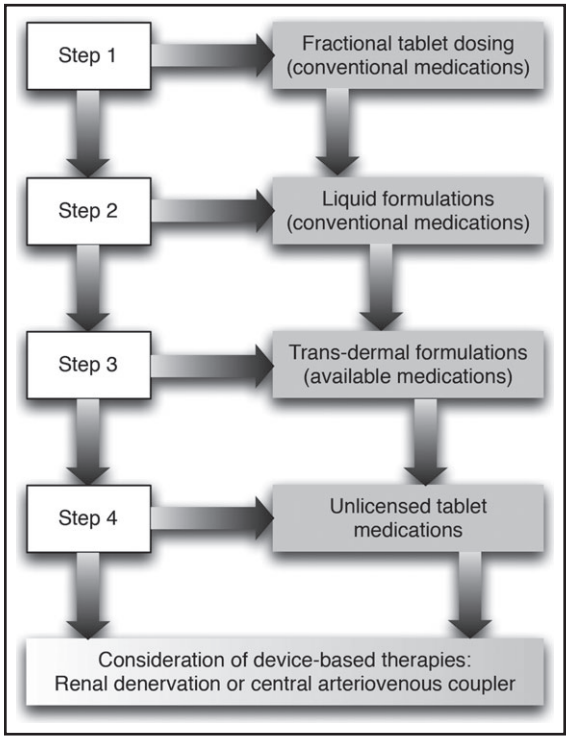

FIGURE 1. Barts multiple drug intolerances to anti-hypertensive medications algorithm.

- Solid formulations (tablets) of conventional guideline-recommended antihypertensive medications at fractional doses (ie, at doses below the minimum solid weight listed in the British National Formulary[26] achieved by halving/quartering tablets with a tablet cutter).
- Liquid formulations of conventional guideline-recommended antihypertensive medications at fractional doses.
- Transdermal preparations of available antihypertensive medications.
- Use of medications not licensed for hypertension and not currently recommended by guidelines.

Starting stepped-care from step 1, prescribing clinicians were free to choose the most appropriate treatment (with no stipulated order of medication class) within each strata of this algorithm depending on the individual patient and patient preference. Medication classes that had previously caused intolerances were re-used within the algorithm unless the patient described a type 1 hypersensitivity allergy previously. Patients were instructed not to continue taking medications that caused unacceptable side effects and to document those adverse reactions and effects on BP and contact our center for further advice.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism v6 (La Jolla, CA) and $P<.05$ was considered significant for all analyses. Data are presented as mean±standard deviation unless otherwise specified. The prespecified coprimary outcomes were change in clinic and home BP after both 6 and 12 months of follow-up. Changes in BP and medication parameters over time were compared by repeated measures analysis of variance with Dunnett's post-hoc tests (to account for multiple comparisons) for comparison to baseline (new patient visit) and Bonferroni post-hoc tests (to account for multiple comparisons) for comparisons between timepoints. Categoric data were analyzed by Fisher's exact test.

RESULTS

Of the 786 new patients referred to Barts BP Centre of Excellence during the period of study, 79 were identified with MDI-HTN. Of these patients, 55 satisfied inclusion and exclusion criteria, and reasons for noninclusion of the remaining 24 are presented in Figure 2.

Patient demographics and baseline characteristics are presented in Table II. Most MDI-HTN patients were referred from primary care by a primary care physician (40%, n=22) but significant proportions were initiated by patients themselves (24%, n=13) or referred from other nonspecialist secondary care physicians (36%, n=20), which was significantly different to the reference population (primary care, n=25; secondary care, n=5 [$P<.01$]). MDI-HTN patients were older ($P<.001$), more likely to be female ($P<.05$), and of white European ethnicity ($P<.01$) than the reference cohort.

There was a high burden of target organ damage (Table III) (as measured by echocardiographic left ventricular hypertrophy) in MDI-HTN patients (55%, n=30), although this was not significantly different to the reference cohort ($P=.51$). MDI-HTN patients had similar levels of renal function measured by sCr ($P=.57$), eGFR ($P=.42$), and nonfasting cholesterol profiles ($P=.47$) to the reference population (Table III). A total of 41% (n=23) and 16% (n=9) of MDI-HTN patients had a coexisting diagnosis of gastroesophageal reflux disease or an anxiety disorder, respectively. Other diagnoses such as autoimmune diseases or diabetes occurred at a frequency of <5%.

MDI-HTN patients were intolerant of numerous medication classes and medicines and were prescribed significantly less medicine than the reference cohort in terms of number of medication classes ($P<.001$), medications ($P<.001$), and WME ($P<.001$) at baseline (Table II). A total of 22% (n=12) of MDI-HTN patients were receiving no antihypertensive medications at baseline, with 6% of MDI-HTN patients on fractional tablet dosing (as defined by the novel algorithm) at referral. No other MDI-HTN patients reported historical treatment with fractional doses prior to referral. In addition, no patients in the reference cohort were on fractional tablet dosing. At baseline, no patients in either the MDI-HTN or reference cohort were on liquid or transdermal formulations of antihypertensive medications. No patients were taking two drugs from within the same class at baseline evaluation.

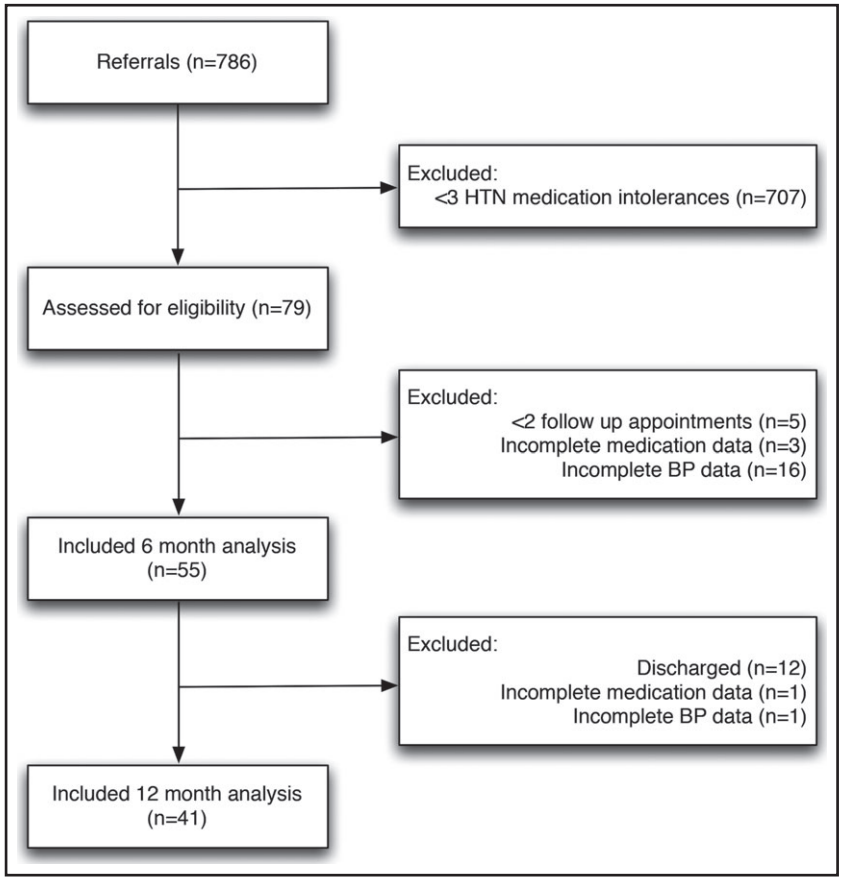

FIGURE 2. Inclusion/exclusion of patients within cohort. BP indicates blood pressure; HTN, hypertension.

While in the reference cohort there was a significant change in clinic BP between referral and first clinical review (−11±20/−8±14 mm Hg, *P*<.01), this was not apparent in MDI-HTN patients (1±10/1±8 mm Hg, *P*=.74). At first clinical review, all patients had significant uncontrolled BP, although MDI-HTN patients had higher clinic SBP (*P*<.001) and DBP (*P*=.06) values compared with the reference cohort (157±19/88±13 mm Hg).

At 6-month follow-up on the novel MDI-HTN treatment algorithm, MDI-HTN patients (n=55) received 3.3±0.5 outpatient visits (including new patient visit) and had initiated 2.9+1.7 algorithm-based medication changes in the previous 6 months.

Clinic BP was reduced by 13±5/5±2 mm Hg (*P*<.05 for both) and home BP was reduced by 11±4/8±3 mm Hg (*P*<.01 and *P*<.05, respectively) (Figure 3). MDI-HTN patients were receiving more medications (2.0±1.2) without increased WME (0.8±0.9) than they were at baseline (*P*<.01 and *P*=not significant, respectively) (Figure 4).

A total of 70% (n=39) of MDI-HTN patients were prescribed a fractional tablet medication in order of frequency: calcium channel blockers (CCBs; n=28), angiotensin II receptor blockers (n=21), mineralocorticoid antagonists (n=21), central sympatholytic agents (n=18), β-adrenoceptor blockers (n=10), thiazide-like diuretics (n=8), and α-adrenoceptor blockers (n=4). Examples of fractional dosing include amlodipine 2.5 mg daily, losartan 12.5 mg daily, spironolactone 6.25 mg daily, moxonidine 100 μg twice daily, atenolol 12.5 mg daily, bendroflumethiazide 1.25 mg daily, and doxazosin 0.5 mg twice daily (Table I).

A total of 40% (n=22) of MDI-HTN patients were prescribed a liquid formulation, with CCBs being prescribed most commonly (91%, n=20), and smaller proportions of patients were prescribed alternative liquid medications, such as mineralocorticoid antagonists (9%, n=5), loop diuretics (5%, n=3), and angiotensin-converting enzyme inhibitors (2%, n=1). Examples of liquid formulations include nifedipine oral solution (OS) 2 mg twice daily, spironolactone OS 5 mg daily, furosemide OS 10 mg twice daily, and ramipril OS 2.5 mg daily.

A total of 16% (n=9) of MDI-HTN patients were prescribed a transdermal formulation of medication, with 11% (n=6) for both transdermal clonidine and glyceryl trinitrate (eg, clonidine TTS1 patch 2.5 mg weekly or glyceryl trinitrate as Minitran patch 5 mg daily). A total of 11% (n=6) of MDI-HTN patients were prescribed a phosphodiesterase inhibitor (eg, tadalafil

TABLE II. Baseline Demographics, Hemodynamic Values, and Medication Use in MDI-HTN and Reference Population

Characteristics	Reference	MDI-HTN
No. (female)	30 (13)	55 (40)
Age, y	47±13	66±9
White-European ethnicity, No.	10	50
Referral mode, No.		
Primary care	25	22
Secondary care	5	20
Self-referred	0	13
Referral office BP, mm Hg		
SBP	168±20	177±25
DBP	96±13	95±16
Intolerances, No.		
Classes	0.2±0.4	5.3±2.1
Medications	0.2±0.4	7.6±3.6
Prescribed medications, No.		
Classes	3.5±1.7	1.4±1.1
Medications	3.6±1.8	1.4±1.1
WME	2.7±1.3	0.8±0.8

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; MDI-HTN, multiple drug intolerances to antihypertensive medication; SBP, systolic blood pressure; WME, whole medicine equivalent. Data are expressed as mean±standard deviation.

2.5 mg daily). At 6 months, 22% (n=12) of MDI-HTN patients were discharged to primary care for further management, while active follow-up was continued in the remaining 78% (n=43, two with missing data for the following 6 months).

After a further 6 months of follow-up (total 12 months) on the novel MDI-HTN treatment algorithm, MDI-HTN patients (n=41) received a further 1.5±0.9 outpatient visits and initiated a further 1.4+1.0 algorithm-based medication change in the previous 6 months. At 12-month follow-up (n=41), clinic BP was reduced from baseline by 17±5/9±3 mm Hg ($P<.01$, $P<.05$) and home BP was reduced by 11±5/12±3 mm Hg ($P<.01$ for both) (Figure 3), while patients were receiving 1.9±1.1 medications delivering 0.7±0.7 WME ($P<.05$ and P=not significant, respectively) (Figure 4).

By 12 months of follow-up of the 41 MDI-HTN patients, 98% (n=40) were prescribed a fractional tablet medication in order of frequency: CCBs (n=26), angiotensin II receptor blockers (n=20), mineralocorticoid antagonists (n=19), central sympatholytic agents (n=14), β-adrenoceptor blockers (n=8), thiazide-like diuretics (n=8), and α-adrenoceptor blockers (n=4). A total of 78% (n=32) of MDI-HTN patients were prescribed a liquid formulation, with CCBs being prescribed most commonly (61%, n=25) and alternative liquid medications, such as mineralocorticoid antagonists (17%, n=7), loop diuretics (10%, n=4), and angiotensin-converting enzyme inhibitors (5%, n=2) less commonly. A total of 49% (n=20) of MDI-HTN patients were prescribed a transdermal formulation of medication, with 37% (n=15) for transdermal clonidine and 20% (n=8) for glyceryl trinitrate. A total of 20% (n=8) of MDI-HTN patients were prescribed a phosphodiesterase inhibitor and 5% were prescribed a long-acting organic nitrate. At 12 months, a further 12% (n=5) of these MDI-HTN patients were discharged to primary care for further management, while active follow-up was continued in the remaining 88% (n=36).

A total of 9% (n=5) of the total MDI-HTN cohort were entered into clinical trial programs of device-based therapies for hypertension within 12 months of follow-up.

DISCUSSION

Antihypertensive medication prevents major cardiovascular events in patients with hypertension[27] but population-level control of BP in treated hypertensive patients is suboptimal.[5] In this study, we described a cohort of patients who were unable to take many classes of antihypertensive medications at conventional doses. We developed and introduced a novel treatment algorithm to enable patients to receive more individualized medicines and significantly reduce BP up to 1 year of follow-up without increasing WME. The prevalence of MDI (to any medications) in the general population is 2% to 5%,[28,29] although in our center over a 24-month period, >10% of all referrals were of patients with MDI-HTN, who on average declared intolerances to five antihypertensive classes and seven antihypertensive medications prior to referral. Recognizing that there are no clinical trials in such groups to provide a high-quality, evidence-based approach, we developed a treatment stratagem around four evidence-based observations.

Firstly, ADRs to most standard antihypertensive medication classes are dose-dependent.[30] We reasoned that prescribing medications at minimal doses (ie, fractional dosing by splitting lowest weight tablet for each medication) and not titrating above usual maintenance doses would allow patients to tolerate medication classes they had previously stopped taking while at higher doses.

Secondly, combination of medications at low doses (between two and four medication classes) has been demonstrated to be additive and achieve a greater BP-lowering effect than increasing monotherapy.[30,31] Thus, we reasoned that by keeping medications at low doses to reduce the chance and/or severity of ADRs and by combining different classes we could still achieve meaningful BP reduction by targeting different physiological regulatory systems involved in cardiovascular homeostasis.

Thirdly, pharmaceutical excipients, required for manufacture of medications as tablets or capsules (such as lactose and silica.), account for 90% of the weight of solid medication formulations[32] and are associated with (especially gastrointestinal) ADRs[33,34] that could possibly explain pharmacodynamically unpredictable

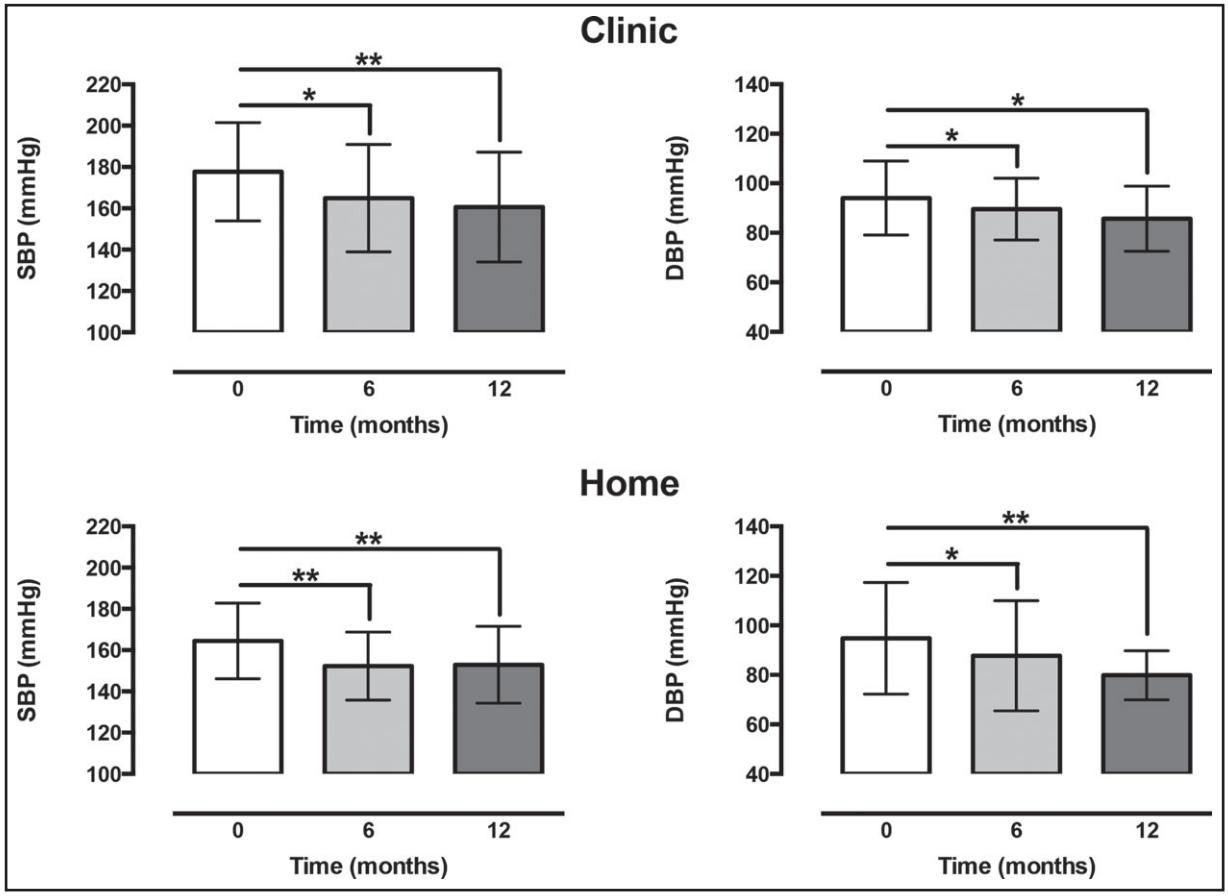

FIGURE 3. Clinic and home blood pressure (BP) at baseline and up to 12 months of follow-up. Data are expressed as mean±standard deviation (n=55 at 0 and 6 months; n=41 at 12 months). Significance shown as **P*<.05 and ***P*<.01 for Dunnett's post-hoc test comparison to 0 months following one-way analysis of variance. DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

reactions reported by patients to unrelated classes of antihypertensive medications. In practice, few excipients are totally inactive or inert in vivo. We reasoned that providing medications in liquid and/or transdermal patch formulation might obviate some of these problems. Transdermal patches can also offer benefits over oral formulations in terms of ease of use, reduce requirements of dosing intervals (eg, once-daily to once-weekly), avoiding first-pass effects (less interactions), as well as avoidance of high maximum plasma levels with rapid changes in drug concentration that may give rise to ADRs that lead to intolerances.

Lastly, we reasoned that repurposing of medications with licensed indications apart from hypertension, such as phosphodiesterase inhibitors and long-acting organic nitrates, which lower BP in small clinical trials,[35,36] could be appropriate in trials of therapy if all else fails. Additionally, we rechallenged patients with medications from the same classes to which they had declared intolerances (but not in cases of type 1 hypersensitivity). Switching within the same class may possibly avoid ADRs in view of the structural differences between similar agents. This strategy for antihypertensive medications has not been largely studied, in comparison to lipid-lowering medications for which intraclass switching is well-established.[37]

Adoption of our stratified medicines approach was associated with large reductions in both clinic and out-of-office BP (home) that were sustained for 12 months in our cohort. These reductions were related to changes in medications that resulted in overall increases in medication classes by approximately 50% per patient but without increasing overall WME; ie, patients were taking more medications but at lower doses than previously. The magnitude of BP reduction at 12 months was similar to that predicted from combining two medications from different classes at half-standard dose (usual maintenance dose, which is <MLD for most medications) of approximately 18/8 mm Hg, using an approximated baseline BP of 180/95 mm Hg.[27] This is a significant reduction in BP, which, if sustained, would lead to large reductions in relative risk of both stroke and ischemic heart disease events by 40% to 60%.[27] In addition, others have demonstrated similar magnitudes of BP reduction in nonselected referral patients (ie, not specific MDI-HTN patients) to hypertension specialist

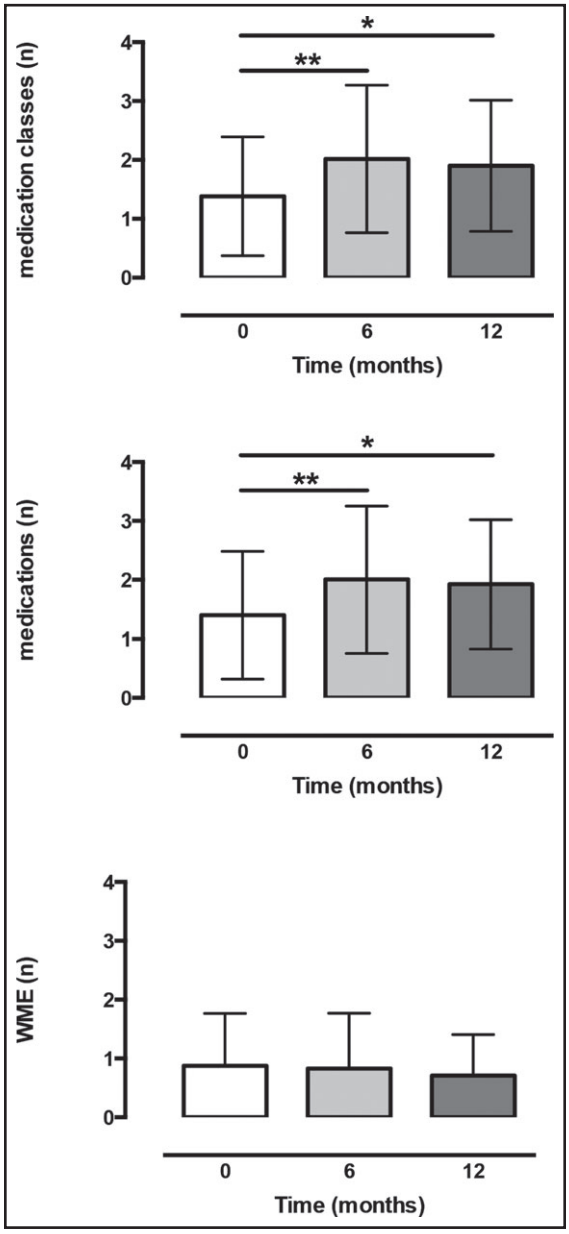

FIGURE 4. Medication use at baseline and up to 12 months of follow-up. Data are expressed as mean±standard deviation (n=55 at 0 and 6 months; n=41 at 12 months). Significance shown as **P*<.05 and ***P*<.01 for Dunnett's post-hoc test comparison to 0 months following one-way analysis of variance. WME indicates whole medication equivalent.

services at 1 year without increasing overall prescribed medication items.[38] While it has previously been demonstrated that adherence is less likely with increasing prescription item numbers,[39] at least in this cohort of patients with multiple previous medication intolerances preventing adherence to antihypertensive therapy at conventional doses, increasing the number of prescription items was associated with improvement in BP. However, our cohort was followed for only a maximum of 12 months and therefore we cannot assume that the responses we have seen will be maintained for longer periods, as the development of medication intolerance, eg, statin-induced myopathy, can occur up to several years after initiation.[40]

TABLE III. Cardiovascular Risk and Comorbidities in MDI-HTN and the Reference Population

Medical Indices	Reference (n=30)	MDI-HTN (n=55)
Target organ damage		
LVH, No. (%)	14 (47)	30 (55)
Renal indices		
sCr, μmol/L	91±35	87±31
eGFR, mL/min	70±19	74±19
Lipid indices		
TC:HDL ratio	3.4±1.2	3.6±0.9
Comorbidities, No. (%)		
GERD	3 (10)	23 (42)
Anxiety disorder	1 (3)	9 (16)
Diabetes mellitus	5 (17)	2 (4)
Autoimmune disease	4 (13)	2 (4)

Abbreviations: eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; LVH, left ventricular hypertrophy; MDI-HTN, multiple drug intolerances to antihypertensive medication; sCr, serum creatinine; TC:HDL, total cholesterol:high-density lipoprotein cholesterol.

In comparison to our randomly selected reference cohort, MDI-HTN patients were almost exclusively of white European ethnicity, which is different than the commonly described ethnicities (black African or black Caribbean) associated with resistant hypertension, and were predominantly female, which is the same as for resistant hypertension.[41] Our study was not able to discern the reasons for these associations. MDI-HTN patients exhibited higher baseline BP and, as expected, fewer prescribed medications at baseline review. It is perhaps surprising that this did not lead to significantly more cardiovascular target organ damage in the MDI-HTN cohort, although we were unable to report on left ventricular mass indexed to body surface area, as this is not routinely reported in our cardiovascular department and we were unable to retrospectively calculate this from two-dimensional echocardiography dimensions because of lack of robust anthropometric data in this dataset. While in the reference population there appeared to be a regression-to-mean or Hawthorne phenomenon between referral and first-review clinic BP, this was not apparent in the MDI-HTN cohort. One possibility is that in patients without medication intolerance, referral to a specialist center was associated with improved adherence and therefore lower BP on first review, although this was not ascertainable in this study.

We demonstrated a four-fold higher prevalence of diagnosed anxiety disorder in our MDI-HTN patients, which is in concordance with previous research in patients with MDI-HTN[42] and patients with MDI to

other medications[21] that suggested increased prevalence of anxiety and panic disorder, depressive, and somatizing traits. These traits may serve to explain some of the nonpharmacologically expected and nonidiosyncratic ADRs that some patients describe, possibly the result of increased propensity to a nocebo response[43] or increased likelihood to report worse severity of ADRs.[44] Importantly, there is no recommended management plan for patients in whom psychological explanations of ADRs are identified.[21,43] In addition, there are other possible organic explanations for apparently non–drug-related ADRs such as mitochondrial toxicity[45] or some patients not tolerating systemic BP reduction because of a lack of effective cerebral autoregulation causing reduced cerebral blood flow.[46] Gastroesophageal reflux disease was four-fold more common in MDI-HTN patients and may explain why some of these patients were able to tolerate more antihypertensive medication classes (in liquid or transdermal formulations) than previously. This may be related to excipients or physiochemical properties of solid dose formulations.

Despite the success of our algorithm, a small subset of patients were enrolled into clinical trials of device-based therapy of hypertension, reflecting that some patients were not able to tolerate any medications within our algorithm or that the amount they could tolerate was insufficient to achieve BP control necessitating further, experimental approaches.

STUDY LIMITATIONS

Limitations of our study include the retrospective nature of the data extraction and collection from electronic and paper patient records and limited length of follow-up, which restricts the ability to draw firm conclusions on future CV risk. Furthermore, we were unable to extract or locate all information relating to previous doses and reasons for patient-specific individual medication intolerances from the patient records and can therefore not comment on proportions of patients with type 1 hypersensitivity and pharmacologically expected or unusual ADRs or determine whether pharmaceutical or pharmacologic (or possibly psychological) mechanisms were responsible for the beneficial effects on BP lowering. We did not confirm adherence to prescribed medications using urine or plasma TDM techniques as our patients had declared overt nonadherence to previously taken medications and therefore we cannot exclude BP reduction attributable to the Hawthorne effect of regular medical interaction rather than increased, tolerated pharmacotherapy. Patients with MDI-HTN probably exhibited higher motivation levels in relation to their CV health given that a substantial proportion self-initiated referral to our service.

In addition, we recognize the imprecise nature of fractional tablet dosing as it cannot be guaranteed that tablets split exactly into half/quarter segments and that some patients also struggled to manage the tablet cutter because of advanced age or concomitant osteoarthropathy. Furthermore, it is clear that undertaking such a treatment algorithm involves multiple points of contact with the clinician and is thus expensive from this perspective as well as entailing use of higher-cost liquid and patch formulations compared with standard off-patent, generic tablets. However, despite these limitations, the demonstrable BP reduction is encouraging and our patients gave positive feedback on this novel approach. We did not routinely use ABP to monitor response to medication changes and therefore we may have missed important pharmacodynamic responses to the use of nonconventional formulations/posology such as liquid nifedipine. Finally, we did not attempt to address the mechanisms of medication intolerance and we accept that in many instances these are unusual and inexplicable and could be linked to personality traits. However, our focus was on providing a management strategy for these often desperate, high-risk patients whose primary care practitioners and other specialists had run out of options to improve their BP and as such we were unable to retrospectively compare our findings with a control cohort of MDI-HTN patients who persisted with standard care.

CONCLUSIONS

A total of 10% of referred patients to a specialist BP center had MDI-HTN, resulting in insufficient pharmacotherapy and significant uncontrolled hypertension. A novel treatment algorithm designed for the management of patients with MDI-HTN, based on fractional tablet, liquid, transdermal antihypertensive medications and the unlicensed use of vasoactive medications was associated with significant increased tolerability of medication classes with concomitant significant BP reduction. Further, prospective studies are required to determine whether this strategy has long-term benefits on BP and cardiovascular morbidity in this difficult-to-treat population.

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