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INSIDE

WHEN THE GOING GETS TOUGH, THE TOUGH GET GOING

This satellite symposium took place on 13th June 2015 as part of the 25th European Meeting on Hypertension and Cardiovascular Protection in Milan, Italy

Chairperson

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Speakers

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MEETING SUMMARY

Patients with elevated blood pressure (BP) represent a major problem for primary care physicians, not only because of the large number of these patients, but also because BP can prove frustratingly difficult to control in some of them. The management of treatment-resistant hypertension (TRH) is indeed a topic of considerable interest over the last few years, particularly since novel, non-pharmacological interventions held out the prospect of helping these patients. The theme of this mini-symposium was how currently available therapeutic tools can be used to manage 'difficult-to-control' patients with persistently elevated BP who may have apparent treatment resistance.

To ensure that this symposium was relevant and practical, invited experts used a patient case in which treatment fails to control BP. One option in such a case might be to assume that the patient has apparent TRH. However, by looking at the case in more detail and carrying out a thorough clinical work-up, other factors such as pseudo-resistance or poor adherence might be playing important roles. The case was used to highlight the importance of investigating the reasons behind a patient's failure to achieve BP control and the steps that can be taken to address these issues.

Professor Josep Redòn introduced the clinical case and discussed the selection of appropriate management strategies and therapies. Estimation of the risk, based on the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) treatment guidelines, and details of the ongoing difficulties in reducing the patient's elevated BP were also covered during his presentation. Professor Michel Burnier discussed in detail difficult-to-control BP and the need for clinical assessment. Among the topics covered were the patient's referral to a specialist treatment centre, apparent resistance to modification/intensification of treatment, detailed investigation to rule out spurious resistant hypertension, assessment of treatment adherence, and development of a plan or management strategy to educate and motivate the patient and improve adherence to treatment. Professor Massimo Volpe

discussed the ongoing management of difficult-to-control patients using strategies designed to favour adherence, including single-pill, fixed-dose combination (FDC) therapy. The meeting was concluded with an interactive discussion, in which the audience raised issues arising from the case presented; these included poor adherence, spurious TRH as a misdiagnosis, and the need for a thorough clinical assessment in order to identify the true cause of the failure to control BP.

Introduction

Professor Massimo Volpe

Hypertension represents a significant global concern in primary care, causing a wide range of severe diseases and comorbidities and a heavy healthcare burden for physicians.[1] Despite the availability of effective antihypertensive agents, BP remains difficult to control and the prevalence of hypertension remains high: hypertension currently affects >1.5 billion people worldwide. According to the most recent international estimates, only 32-47% of primary care patients have a systolic/diastolic BP <140/90 mmHg (<130/80 mmHg for diabetics), as recommended by the International Guidelines Recommendations.[2,3]

Studies have reported the need to implement strategies to improve hypertension in primary practice in European countries.[2,3] In a comprehensive analysis of clinical data collected from two hypertension surveys of >200,000 patients conducted between 2000 and 2011, the rates of sub-optimal BP were high across all clinical settings, including the general practice (36%), hospital or outpatient clinics (24%), and hypertension units and excellence centres (16%).[3]

Barriers to effective management of hypertension can be complex. While hypertension can cause a wide range of severe diseases and comorbidities, the patient's response to pharmacotherapy varies. To help guide management, patients with hypertension can be classified as 'easy-to-treat' (BP controlled with <3 antihypertensive medications) or 'difficult-to-control' (BP uncontrolled with ≥3 antihypertensive medications; often diagnosed as being drug-resistant). Difficult-to-control patients are at high risk of cardiovascular (CV) problems (e.g. heart attack, stroke) and, although usually referred to specialised units and clinics, BP levels and rates of control in these populations remain sub-optimal.[3-5]

By looking at a real-life clinical case, this meeting aimed to: (1) evaluate the challenges commonly encountered in the management of hypertensive patients: the 'difficult-to-control' patient with persistently elevated BP; (2) highlight the importance of thoroughly investigating the patient to determine whether pseudo-resistance or poor adherence might underlie the failure to lower BP; and (3) evaluate practical steps for improving the management of such patients, and which can help them to achieve BP control.

Building a Real-Life Patient Case Treatment: A 58-Year-Old Man with Grade 2 Hypertension

Professor Josep Redòn

In his initial presentation, Prof Redòn introduced the case study: a 58-year-old man who arrived at the clinic for a regular check-up. The patient was diagnosed with Grade 2 hypertension based on the following clinical history:

Clinical history

Family history of hypertension and renal failure of unknown origin in his father

Personal history

- 58-year-old man, asymptomatic
- Hypertension diagnosed 10 years before without regular antihypertensive treatment
- At the time of the visit, amlodipine (AML) 10 mg once daily (qd) had been administered for the previous 2 months
- Stopped smoking 5 years before attending the clinic, occasional alcohol intake
- Sedentary lifestyle

Physical examination

- Office BP (average of three measures): 162/98 mmHg
- Heart rate (HR): 76 beats per minute (bpm)
- Weight: 86 kg; body mass index: 31 kg/m^2; waist: 103 cm
- No murmurs were heard in the chest
- No abdominal masses or murmurs were detected
- Peripheral pulses were normal and symmetrical
- No ankle oedema
- Ankle/brachial index: 0.97

CV risk assessment

Metabolic profile

- Glucose: 6.2 mmol/l (112 mg/dl)

- HbA_{1c}: 6.1%
- K^+: 4.2 mmol/l
- Total cholesterol: 4.5 mmol/l (173 mg/dl)
- High-density lipoprotein (HDL) cholesterol: 0.9 mmol/l (35 mg/dl)
- Triglycerides: 2.2 mmol/l (195 mg/dl)
- Uric acid: 0.5 mmol/dl (7.8 mg/dl)
- Oral glucose tolerance test 2-hour: 7.8 mmol/l (141 mg/dl)

Evaluation of organ damage*

Kidney

- Serum creatinine (SCr): 116.7 mmol/l (1.3 mg/dl)
- Estimated glomerular filtration rate (eGFR): 53 ml/min/1.73 m^2
- Microalbuminuria, albumin-to-creatinine ratio (ACR): 87 mg/g

Heart

- Electrocardiogram: voltage left ventricular hypertrophy (LVH) without strain
- Echocardiogram: posterior wall thickness: 12 mm
- Left ventricular mass index: 144 g/m^2
- Ejection fraction: 50%, symmetrical contractility

Out-of-office BP values†

24-h ambulatory BP monitoring (ABPM)

- Average 24-hour: 149/92 mmHg, HR: 68 bpm
- Average awake: 156/97 mmHg, HR: 80 bpm
- Average sleep: 142/89 mmHg, HR: 62 bpm

*According to the ESH/ESC treatment guidelines, electrocardiography, eGFR, and microalbuminuria are mandatory for the assessment of organ damage. For better assessment, echocardiography plus Doppler is also used.[5]

†Out-of-office BP should be considered to confirm diagnosis of hypertension, identify the type of hypertension, detect hypotensive episodes, and maximise prediction of CV risk (Class IIa, Level B). Home BP monitoring or 24-hour ABPM may be considered depending on indication, availability, ease, cost of use, and, if appropriate, patient preference (Class IIb, Level C).[5]

The case represents a patient with a high risk of CV adverse events:

A patient with high risk of CV adverse events

- Grade 2 hypertension (systolic BP: 160-179 mmHg, diastolic BP: 100-109 mmHg)
- Target organ damage in the two organs assessed: LVH, chronic kidney disease (low eGFR and microalbuminuria)
- Abnormal fasting glucose/glucose intolerance
- Low HDL cholesterol
- 10-year absolute risk of 20-30% for CV events (Framingham) and of 5-8% for mortality (SCORE)[6]

Treatment approach

- Lifestyle changes with BP drugs targeting <140/90 mmHg[5]

Follow-up

- Dietary advice, physical exercise
- AML 10 mg qd + olmesartan (OLM) 40 mg qd
- 4 weeks later:
  - The patient started with a single-pill, FDC of AML 10 mg qd + OLM 40 mg qd + hydrochlorothiazide (HCTZ) 25 mg qd
  - BP: 158/101 mmHg
  - Weight: 84 kg
  - Fasting glucose: 6.1 mmol/l (110 mg/dl)
- 8 weeks from the beginning:
  - BP: 152/96 mmHg
  - Weight: 83 kg
  - Fasting glucose: 6.0 mmol/l (109 mg/dl)
- Evaluation of kidney damage:
  - SCr: 124.7 mmol/l (1.4 mg/dl)
  - eGFR: 53 ml/min/1.73 m^2
  - Microalbuminuria, ACR: 67 mg/g

The patient was referred to a hypertension clinic (discussed by Prof Michel Burnier)

Difficult-to-Control Blood Pressure and the Need for Clinical Assessment

Professor Michel Burnier

Patient history (referred to a hypertension clinic)

- A 58-year-old man with uncontrolled hypertension despite treatment with AML 10 mg qd, OLM 40 mg qd, and HCTZ 25 mg qd
- Office BP still elevated and recent ABPM abnormal
- No need to repeat laboratory assessments (recent laboratory values)
- Target organ damage and high CV risk
- Apparent TRH based on the ESH/ESC guideline definition[5]

Diagnosis – management of true versus apparent TRH step by step

- Confirm the correctness of the diagnosis
- Confirm the correctness of the doses
- Existence of interfering factors, i.e. factors that reduce the efficacy of drugs to lower BP: NaCl intake (based on a 24-h urine collection), non-steroidal anti-inflammatory drugs, administration of drugs that increase BP (cyclosporine, erythropoietin), obesity, high alcohol consumption, sleep apnoea syndrome
- Concomitant medications
- Existence of a secondary form of hypertension

Adherence to treatment

- Adherence questionnaire: low score on the 4-question Morisky questionnaire[7]
- Prescription record review: lack of renewal of prescriptions
- Patient was non-adherent

According to some studies, adequate treatment of patients with apparent TRH is sub-optimal. In a community-based practice network study, only 15% of patients with apparent TRH were receiving adequate treatment (diuretics and ≥2 other drugs with ≥50% of maximum approved dose).[8] However, ABPM may be used to rule out 'white-coat hypertension' in more than one-third of apparent TRH cases.[9] These results highlight that hypertension control could be improved by prescribing more optimal pharmacotherapy for uncontrolled hypertension, including apparent TRH.

Poor adherence to antihypertensive drug therapy is one of the main causes of unsatisfactory control of BP and a common cause of apparent TRH.[7,10] In a longitudinal database study involving clinical studies conducted between 1989 and 2006, more than half of the patients discontinued their treatment during a 12-year period. In clinical practice, invasive (e.g. measurements of drugs and biomarkers) and non-invasive (e.g. patient interview, electronic monitoring) methods can be used to assess adherence to treatment (Figure 1). Among these tools, asking the patient and accepting their responses is key in assessing adherence. However, accurately monitoring adherence in the long term can be difficult.

Poor adherence is also a common cause of apparent TRH.[10] Treatment adherence can be assessed by toxicological urine screening, in particular when a multidrug regimen is a cause of apparent resistant hypertension.[10] Electronic monitoring of drug adherence is also a useful approach to identify and correct adherence problems in TRH, and can considerably enhance the efficacy of antihypertensive therapy in patients with uncontrolled hypertension.[11] As observed in other therapeutic fields, 'white-coat adherence' is also seen in hypertensive patients in whom the progressive decline in drug adherence is rapidly reversed during the 3 days preceding the medical visit.[12]

Factors affecting adherence include the disease (severity, symptoms), patient (personality, lifestyle, beliefs), treatment (number of doses, duration, side-effects), pharmacist (understanding recalls), physician (information, explanations), and therapeutic goals. The role of adherence is particularly important when treatments do not provide the expected clinical results, as can be the case in hypertension. Since a lack of adherence is a potential cause of resistant hypertension, it is important to focus on drug adherence to improve BP control in these populations (Table 1).[13]

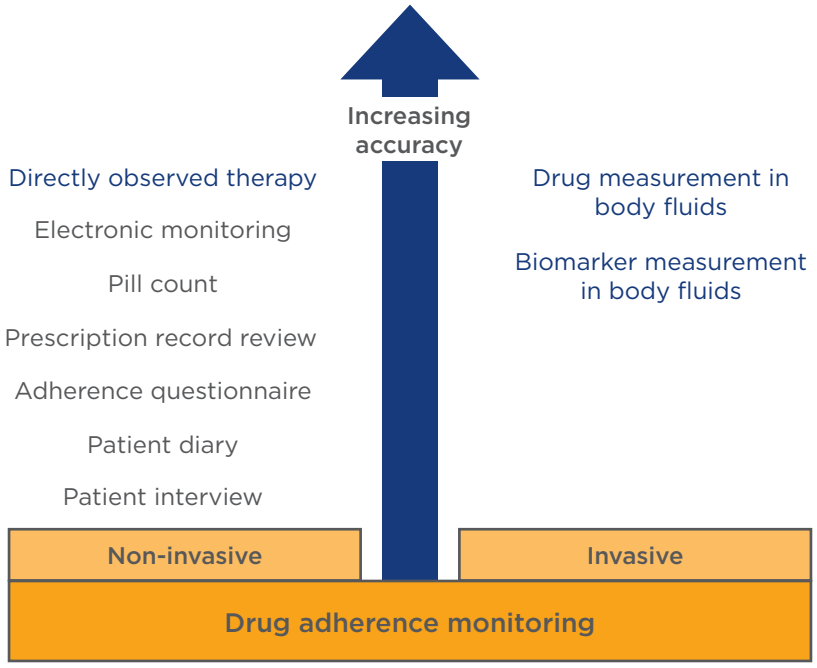

Figure 1: Long-term drug adherence is difficult to monitor.

Table 1: Addressing poor adherence.[13]

		Drug adherence	
		Adequate	Poor
Therapeutic goals	Achieved	Educative value	Reduce therapy and/or question diagnosis
	Not achieved	Change treatment and/or perform investigations	Support complicance, no change in therapy

In summary, practical aspects to improve adherence include:

1. Detecting poor adherence by talking about non-adherence (increase awareness of the problem), monitoring the treatment whenever possible, identifying and contacting patients who are not showing up at consultations, and focussing on patients in whom therapeutic goals are not achieved
2. Prevention of poor adherence by giving convenient appointments, simplifying and adapting the treatment, giving individualised instructions, and promoting the patient's collaboration with treatment
3. Maintaining or improving adherence by supervising the treatment, associating pill taking with daily activities, providing feedback on treatment to the patient, and positive reinforcement of adherence

Nevertheless, it should be noted that no single intervention is truly superior in maintaining adherence and studies have failed to identify tools and methods that could enhance medication. The results of these studies were statistically heterogeneous and appear to be inconsistent.

Managing a Difficult-to-Control Patient

Professor Massimo Volpe

Treatment after assessing poor adherence

- Reinforce any advice regarding diet, lifestyle, and medications
- Patient participation (diary and home BP monitoring)
- Shift to a 'simplified treatment' with a fixed combination of AML 5 mg/OLM 40 mg/HCTZ 12.5 mg qd in a single-pill FDC (AML/OLM/HCTZ)
- Four weeks later:
  - Office BP: 136/82 mmHg
  - HR: 76 bpm

Single-pill combination therapies have the potential to increase adherence compared with separate single pills.[14] In patients for whom a non-adherent issue to the single-pill FDC of AML/OLM/HCTZ medication is clear, a low-dose pill may be recommended.

What are the benefits of treatment simplification?

Treatment simplification is one of the most straightforward ways to improve adherence. Complicated treatment regimens have been shown to be a major contributory factor to poor patient adherence.[15] Reducing pill burden through the use of FDC therapy can therefore play an important role in improving adherence.[16] A meta-analysis showed that, compared with free-drug combinations, FDCs significantly improve adherence (by 29%).[17]

Variation in the appearance of generic pills is associated with non-persistent use of essential drugs after myocardial infarction among patients with CV disease.[18] These results raise the importance of considering the appearance of the pills when addressing adherence. Combination therapies can also provide important benefits for treatment initiation, particularly in patients who are at high risk of adverse CV events and need early BP control.[19] Mazzaglia et al.[20] demonstrated that a high adherence rate to antihypertensive treatment is associated with a reduction in CV events among newly diagnosed hypertensive patients. The appropriate use of antihypertensive drugs is associated with a long-term reduction in acute CV events.

In clinical practice, a single-pill platform of OLM in combination with AML and/or HCTZ improves adherence in the majority of patients with hypertension (Table 2).[21]

Patient status 6 months later

- Ongoing treatment with the single-pill FDC of AML/OLM/HCTZ

- Periodic reinforcement of adherence
- Office BP: 138/80 mmHg
- Home BP: 129/76 mmHg
- Weight: 81 kg
- Fasting glucose: 5.7 mmol/l (102 mg/dl)
- HbA_{1c}: 6.1%
- eGFR: 54 ml/min/1.73 m^2
- Microalbuminuria, ACR: 20 mg/g

The continuation of the current therapy over a single-pill dual therapy (AML 5 mg/OLM 40 mg) was selected as the appropriate therapy according to BP control and laboratory values.

In summary, checking adherence and using simple treatments are both key tools that should be considered in order to improve management of hypertension.

Table 2: Angiotensin receptor blocker (ARB) single-pill platform: hypertensive patients with specific risk factors, subclinical organ damage, or overt organ damage.[21]

	Grade 1 (systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg)	Grade 2 (systolic BP 160-179 mmHg or diastolic BP 100-109 mmHg)	Grade 3 (systolic BP ≥180 mmHg or diastolic BP ≥110 mmHg)
No risk factors	OLM 10-20 mg	OLM/AML 20/5 mg*	OLM/AML 20-40/10 mg*
		OLM/HCTZ 20/12.5 mg*	OLM/HCTZ 20-40/25 mg*
Specific risk factors/subclinical organ damage			
Dyslipidaemia, hyperuricaemia, obesity, or metabolic syndrome	OLM 10-20 mg	OLM/AML 20/5 mg*	OLM/AML 20-40/5-10 mg*
Fit elderly, <80 years old	OLM 10-20 mg if well tolerated	OLM/HCTZ 20/12.5 mg*	OLM/HCTZ 20-40/25 mg*
Frail elderly, >80 years old, SBP ≥160 mmHg	Consider OLM 10-20 mg	OLM/HCTZ 10-20/12.5 mg*	OLM/HCTZ 20-40/25 mg*
Atherosclerosis, arteriosclerosis, or PAD	Consider OLM 10-20 mg	OLM/AML 20-40/5 mg	OLM/AML 20-40/10 mg
LVH	OLM 20-40 mg	OLM/HCTZ 20-40/12.5 mg*	OLM/HCTZ 20-40/25 mg*
Microalbuminuria/ proteinuria (CKD Stage ≤3)	OLM 20-40 mg	OLM/AML 40/5 mg	OLM/AML 40/10 mg
Diabetes	OLM 20-40 mg	OLM/AML 40/5 mg*	OLM/AML 40/10 mg*
Overt organ damage			
Atrial fibrillation	OLM 20-40 mg	OLM/HCTZ 20-40/12.5 mg	OLM/HCTZ 20-40/25 mg
Nephropathy (CKD Stage >3) eGFR <30 ml/min/1.73 m^2	OLM 20-40 mg	OLM/AML 40/5 mg	OLM/AML 40/10 mg
Coronary artery disease	OLM 10-20 mg	OLM/HCTZ 20-40/12.5 mg*	OLM/HCTZ 40/25 mg*
Previous stroke or transient ischaemic attack	OLM 10-20 mg	OLM/AML 20-40/5 mg*	OLM/AML 20-40/10 mg*
Heart failure with reduced EF	OLM/HCTZ 10-20/12.5 mg	OLM/HCTZ 20-40/12.5 mg*	OLM/HCTZ 20-40/25 mg*

*Consider single-pill triple combination if BP is not at target.
BP: blood pressure; PAD: peripheral arterial disease; LVH: left ventricular hypertrophy; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; EF: ejection fraction; OLM: olmesartan; HCTZ: hydrochlorothiazide; AML: amlodipine.

Summary and Conclusions

Professor Massimo Volpe

Concerns arising from this patient case include the initial failure to detect poor adherence and the misdiagnosis of true TRH, both of which are problems frequently encountered with hypertensive patients.

Recommended solutions include:

1. Elucidating the cause of the persistently elevated BP
2. Using ABPM to rule out apparent TRH
3. Ruling out white-coat adherence
4. Discussions with the patient to determine the level of adherence
5. Physician–patient interaction and engagement

Addressing poor adherence in order to lower BP and bring it under control can be achieved by:

1. Simplifying the regimen by reducing the pill burden
2. Using single-pill dual and triple combinations based on a platform of effective and well-tolerated ARBs, such as OLM

The case study illustrates a type of problem frequently seen among hypertensive patients, with an initial failure to detect poor adherence being incorrectly diagnosed as TRH.

- Close examination of the case revealed that the patient's persistently elevated BP was due to poor adherence. By working with the patient and paying close attention to this issue it was possible to lower the patient's BP and bring it under control.
- The use of single-pill dual and triple combinations based upon effective and well-tolerated ARBs such as OLM is relevant in such a case because keeping pill burden to a minimum is likely to encourage the patient to adhere to treatment.

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MANAGEMENT OF BLOOD PRESSURE CONTROL: AT THE CUTTING EDGE

This satellite symposium took place on 29th August 2015 as a part of the European Society of Cardiology Congress 2015 in London, UK

Chairperson

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MEETING SUMMARY

Prof Williams opened the symposium by discussing the current state of blood pressure (BP) control in Europe and the key barriers to improving BP control rates. Prof Weiss presented the 'Low BP in Vienna' initiative that has been initiated in Austria in order to improve BP control. Prof Mourad discussed the ongoing campaign to improve BP control rates in France, and Prof Volpe presented a case study of an elderly patient with hypertension and chronic kidney disease (CKD). Prof Parati concluded the symposium by commenting on the improvements in technology with respect to BP control.

The meeting objectives were to review the current achievement of BP goals in Europe since 2008; to evaluate the 70% BP goal initiatives in France and Italy; to use practical examples to assess the use of single-pill fixed-dose combinations (FDCs); and to assess the impact of technological advances on BP control.

Chairperson's Introduction: What Are the Key Barriers That Are Holding Back Improvements in Blood Pressure Control in 2015?

Professor Bryan Williams

Rates of BP control (BP <140/90 mmHg) are suboptimal in the majority of countries across Europe, with many countries having a control rate <50%.[1-3] Barriers to achieving optimal BP control, identified in the 2013 guidelines from the European Society of Hypertension (ESH) and European Society of Cardiology (ESC), include therapeutic or physician inertia; low patient adherence to therapy; and deficiencies within the healthcare systems that do not encourage or allow for a system-wide approach to improving treatment.[4] Achieving good BP control will result in significant savings to the healthcare economy, despite the costs of therapy. In the USA, 56,000 fewer cardiovascular events and 13,000 fewer deaths would occur each year if previously untreated patients were treated according to the guidelines.[5,6]

Non-adherence to treatment is a significant issue and may have significant consequences in this high-risk illness. A study of 367 patients with uncontrolled hypertension, including 108 with treatment-resistant hypertension, showed that, of the patients with uncontrolled BP (n=76) on ≥4 drugs, half (53%) were non-adherent, of whom 30% demonstrated complete non-adherence to treatment when blood drug levels were tested.[7] A direct relationship has been demonstrated between the number of drugs that a patient is prescribed and the likelihood of the patient being adherent, with patients on more medications being less likely to adhere to therapy (Figure 1).[8]

A simplified treatment approach, such as the Simplified Therapeutic Intervention to Control Hypertension (STITCH)-care algorithm used in Canada, may be a potential solution to non-adherence. A study has demonstrated significantly improved levels of BP control using the STITCH-care algorithm, in which patients were started on treatment with a combination of two treatments with subsequent up-titration of dose and addition of further diuretics in a step-wise approach, compared with the usual standard of care.[9] Similarly, a study in which patients were allowed to self-monitor their BP and up-titrate their own medication according to an algorithm found highly significant improvements in BP control compared with patients being managed by their regular physician.[10,11]

Non-adherence	New referrals	Follow-up	Referral renal denervation
% complete	8.8	9.1	23.5
% partial	9.6	28.8	0
Any	18.4	37.9	23.5

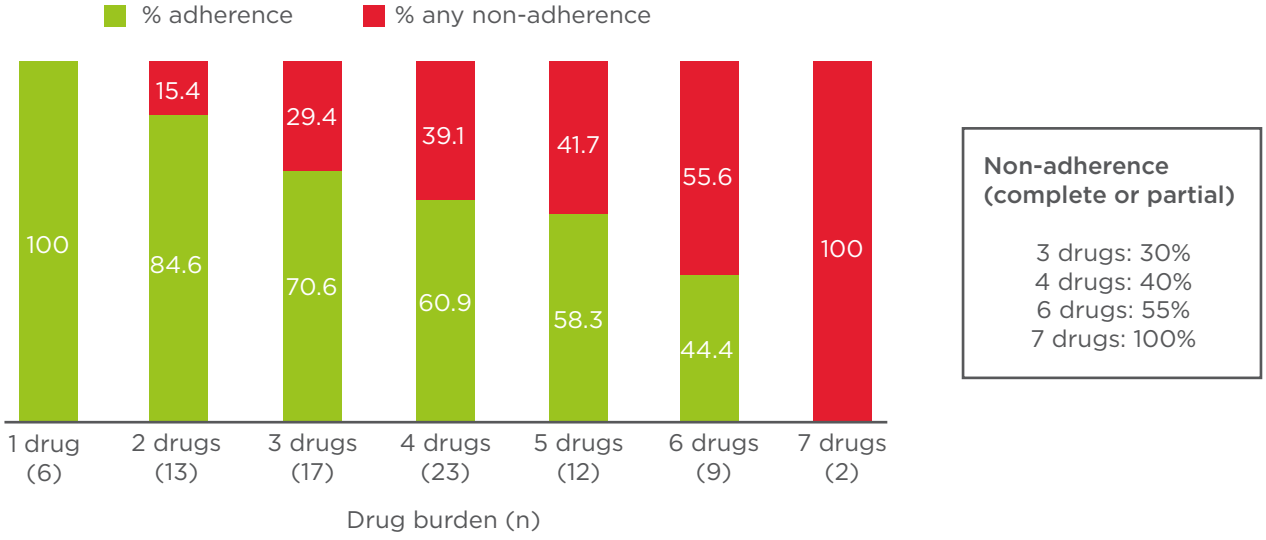

Figure 1: Blood drug-detection levels and adherence.[8]

Although efficacy of available medications has been demonstrated, two important questions remain: how can we encourage patients to take the medications, and how do we encourage the physicians to prescribe them?[12]

Blood Pressure Parameters Today: Has There Been Any Change Since 2008?

Professor Thomas Weiss

A white paper was published in 2008 in response to the suboptimal rates of BP control across Europe,[13] and which encouraged physicians to drive awareness of the dangers of hypertension, increase patient education, encourage patients to be more accountable for their health, and to simplify treatment. In comparison with European rates of BP control that range from 17–46%,[14-16] Canada has demonstrated superiority with 65% of patients achieving optimal control.[17] However, implementation of disease management programmes has improved rates of BP control in several European countries.[1-3]

In Austria, a prospective registry that includes approximately 10,000 patients has commenced in collaboration with the Pharmacists College Vienna (urban) and Lower Austria (rural). All patients with a prescription for an antihypertensive drug are included. Information collected includes BP, socioeconomic data, comorbidities, and comedications. These data will be used to obtain information on the types of antihypertensive medications that are prescribed and the percentages of patients with controlled BP, and will permit various comparisons such as BP control in rural versus urban areas.

In parallel with the registry, a hypertension management programme, 'Low BP in Vienna',[18] is being developed that aims to: enhance BP control in primary care; raise general practitioner (GP) awareness of BP control; introduce GPs to standardised and simplified titration measures with single-pill FDCs; provide data on BP control in primary care in Vienna; and identify patients with treatment-resistant hypertension.

The study is based on two concepts. Firstly, it aims to use an effective intervention in the general population as per the Canadian STITCH study. According to the STITCH algorithm,[9] a patient with uncontrolled hypertension starts on an angiotensin-converting enzyme (ACE) inhibitor and diuretic, or an angiotensin receptor blocker (ARB) and diuretic.

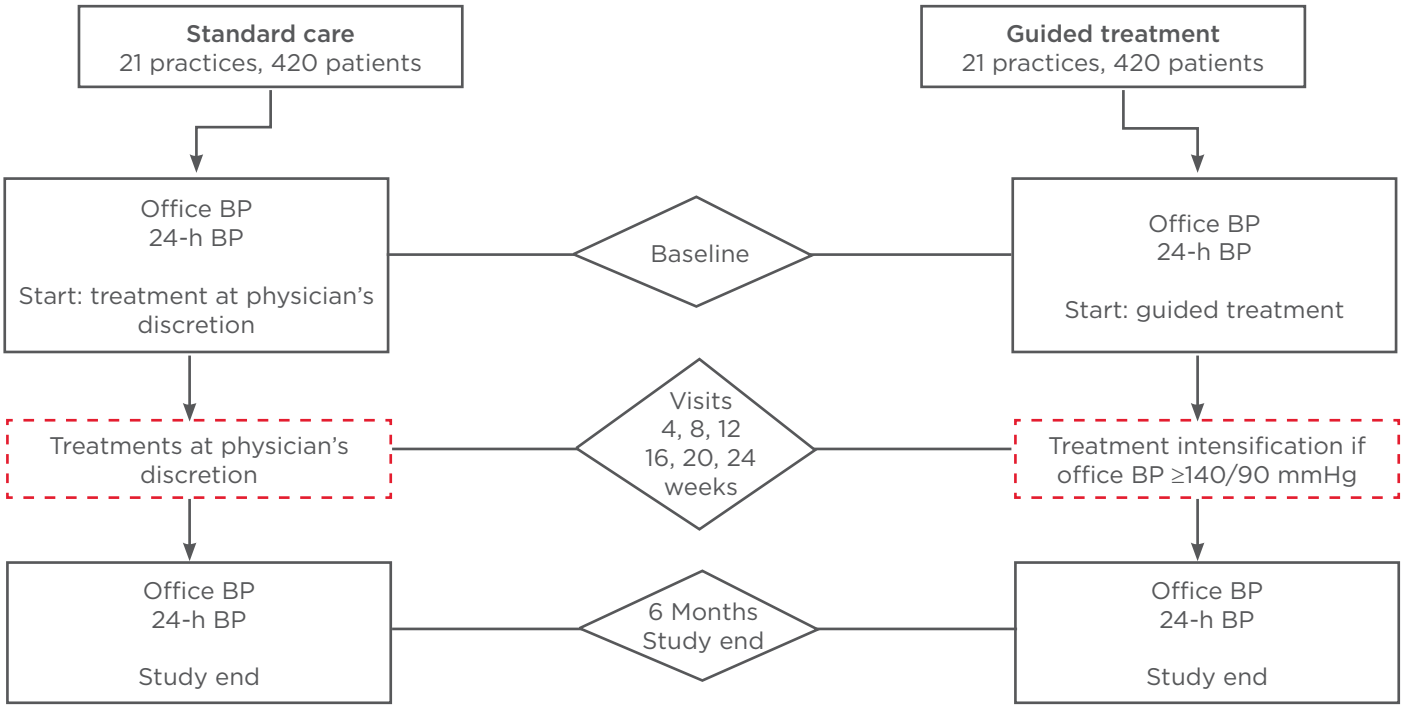

Figure 2: Low BP in Vienna study design.
BP: blood pressure.

If BP is not controlled, the medications are up-titrated to the highest dose. A calcium channel blocker (CCB) may be added and up-titrated, followed by an alpha or beta-blocker or spironolactone, if treatment remains unsuccessful. The second concept involves the use of a simple treatment regimen that is easy for the doctor and for the patient. The BP Control in all Subgroups with Hypertension (BP-CRUSH) trial evaluated olmesartan and amlodipine, prescribed at the lowest dose, using single-pill FDCs throughout the treatment regimen, resulting in maximum doses of olmesartan, amlodipine, and hydrochlorothiazide of 40 mg, 10 mg, and 25 mg, respectively.[19] The high level of BP control (90%) achieved in this trial may not be achievable in a real-world setting. However, even a smaller improvement will still be very important.

In the Low BP in Vienna trial, 840 patients from 42 practices have currently been included and results are expected in approximately 1 year. Physicians are randomised 1:1 to provide standard of care or the guided treatment protocol (Figure 2).

For standard of care, the treatment regimen is at the physician's discretion. Monthly visits are recommended but not protocol-mandated. In the guided treatment arm, treatment intensification is conducted as per the study's algorithm, based upon the BP-CRUSH algorithm[19] if office BP is above 140/90 mmHg. Patients begin with the lowest possible single-pill FDC of olmesartan and amlodipine, which is then up-titrated to the maximum dose of the triple therapy comprising olmesartan, amlodipine, and hydrochlorothiazide using single-pill FDCs throughout. Patients already taking antihypertensive medications start at different points in the algorithm, depending on their medical history. The primary endpoint is the proportion of patients with an office BP under 140/90 mmHg after 6 months; the secondary endpoint is improvement in 24-hour BP profile after 6 months.

Although there has been much improvement since 2008, 100% BP control has not yet been achieved. The 2008 white paper is currently being updated, with a focus on: achieving the BP target of <140/90 mmHg; reducing inertia to treatment intensification; simplifying treatment, e.g. through the use of FDCs; improving patient empowerment; and involving other stakeholders in the control of BP.

How Have Initiatives Implemented in France and Italy to Achieve 70% Blood Pressure Control Among Treated Hypertensives Changed the Situation?

Professor Jean-Jacques Mourad

The French Ministry of Health began a campaign against stroke in 2012, the objective of which was to achieve BP control rates of 70% by 2015.[20] Although the rate of BP control (45%) was good in comparison with some other countries, it was felt that the newer recommendations were not making any further improvements in BP control in France. The campaign aimed to focus on the two main barriers to improvement in terms of BP control rates: inertia with regards to treatment intensification and non-adherence to current therapies. The campaign's guidelines stated that patients' BP should be controlled within a 6-month period after initiation of antihypertensive therapy. If this was not possible, patients were to be referred to a specialist. It was recommended that GPs should switch to combination therapy after initial failure with monotherapy, preferably using an FDC. In addition, it was highlighted that at least one-third of patients require triple therapy, and it was recommended that triple therapy should be proposed if the patient was not controlled by two different combination therapies at different dosages. The campaign's seven key points were included in a booklet that was released in 2012.[20]

In a survey conducted in the general French population in 2006, the global BP control rates in patients aged 18–74 years were around 50%, with generally more female patients being controlled from age 45 years onwards.[21] The survey also identified an over-reliance on monotherapy, with 36% of patients treated with just one drug, of which only 35% were uncontrolled.

Surveys conducted in GPs' offices in 1994 and 1999 showed that almost one in two patients entering GP offices in France were hypertensive and that only 32% of patients were achieving the target of hypertension treatment in 1999.[22] A similar survey conducted in 2014 involved 1,000 GPs working in France (the PASSAGE Survey).[23] The GPs were requested to include the first consecutive 20 hypertensive patients that entered their offices from autumn to winter 2013/2014. The definition of BP control was set as BP <140/90 mmHg for all patients, excluding patients aged >80 years in

whom systolic BP should be <150 mmHg. BP control rates were comparable with results from recent surveys conducted in the general population. The majority of elderly hypertensive patients in France were on target, likely due to the increased threshold for BP control in this group. Interestingly, the number of antihypertensive treatments used seemed to be the only modifiable factor that was positively associated with BP control.

A similar initiative in Italy that aims to achieve BP control in 70% of treated patients recommends more extensive use of dual or triple combination therapy, and advocates for the use of single-pill combinations to improve adherence and maintain optimal BP control.[24]

Has the Introduction of Single-Pill Fixed-Dose Combinations Affected Blood Pressure Management? Presentation of a Patient Case: The Elderly Patient with Chronic Kidney Disease

Professor Massimo Volpe

Prof Volpe presented the case of an elderly patient with hypertension and CKD. The patient was male, 74 years old, and of normal height, weight, and body mass index. He was a former smoker with a relatively high cardiovascular risk profile, including hypercholesterolaemia treated with atorvastatin, and carotid atherosclerosis treated with aspirin. There was mild renal impairment. The patient had a 20-year history of hypertension, which had been treated mostly with a beta-blocker, diuretic, and dihydropyridinic CCB. Home BP control was poor and the patient had fatigue. The referring physician added an ACE inhibitor (low-dose ramipril) and titrated the dosage of the CCB to twice daily (BID). The patient stopped treatment as he felt no improvement in BP control and thought there were too many pills to take.

Upon referral, the electrocardiogram findings indicated that the patient was likely to have future atrial fibrillation or heart failure. Renal artery ultrasound was relatively normal and carotid artery ultrasound showed a mild increase of the intima–media thickness, without haemodynamic effects. The creatinine level was 1.5 mg/dL, with an estimated glomerular filtration rate of 49 mL/min/1.73 m^2. Cholesterol was well controlled and the patient had mild albuminuria and microalbuminuria of 37 mg/24 hours.

Home BP was 160/80 mmHg and office BP was 168/88 mmHg. The patient had a heart rate (HR) of 64 beats per minute (bpm). Daytime (159/81 mmHg) and night-time (136/74 mmHg) 24-hour BPs were abnormal. The patient was taking atenolol 50 mg as half a pill BID, chlorthalidone 25 mg, nifedipine slow release 30 mg BID, aspirin, atorvastatin, and a proton-pump inhibitor. The patient was determined as high-risk, with predominantly systolic hypertension resistant to multiple drug combination therapies, and mild CKD.

Use of ACE inhibitor-based therapy in the Hypertension in the Very Elderly Trial (HYVET) reduced the risk of death and stroke,[25] while data from the Losartan Intervention for Endpoint Reduction (LIFE) trial showed that, in a cohort of patients with isolated systolic hypertension, ARB therapy resulted in a significant reduction in the composite primary endpoint (cardiovascular death, stroke, or myocardial infarction) and total mortality.[26] A recent meta-analysis showed that use of renin–angiotensin system (RAS) blockers is one of the most effective BP-lowering strategies to provide renal protection.[27] ARBs were shown to provide significant protection against the development of end-stage renal disease, and also promote regression of albuminuria; this effect was even stronger with a combination of ARBs and CCBs.[27]

A practical, individualised platform has been developed to identify antihypertensive strategies using a single-pill, ARB-based combination therapy.[28] Based on this strategy, the current case of an elderly patient with isolated systolic hypertension could benefit from a combination of an ARB with hydrochlorothiazide. With respect to the microalbuminuria and nephropathy observed in this patient, the patient may also benefit from a combination of an ARB and CCB. Triple therapy may also be useful if control is not achieved on dual therapy. ARBs have been shown to be efficacious in elderly patients. The Efficacy and Safety in elderly Patients with Olmesartan medoxomil versus Ramipril Treatment (ESPORT) trial found a significant improvement in 24-hour BP control with olmesartan compared with ramipril in elderly patients.[29]

The fatigue experienced by the current patient could have been related to his treatment with

beta-blockers. Therefore, chlorthalidone and nifedipine were discontinued and single-pill FDC therapy with olmesartan 20 mg and amlodipine 5 mg was commenced. At 1-month follow-up, there were no relevant side effects or adverse reactions, home BP was 150/70 mmHg, office BP was 152/82 mmHg, HR was 64 bpm, and creatinine level was more or less unchanged. Olmesartan and amlodipine were titrated to 40 mg and 5 mg, respectively. At 6-month follow-up, the patient reported fatigue as having a major impact on his quality of life and wished to take fewer pills. The beta-blocker was discontinued and a thiazide diuretic was directly combined with the ARB and CCB in a single pill as a triple therapy.

After 9 months of treatment, home BP and office BP had improved. Creatinine remained similar and 24-hour BP was satisfactory. This study highlighted the potential utility of ARB-based therapy for poorly controlled hypertension in elderly patients with CKD, and also the importance of single-pill FDCs in non-adherent patients. The practical platform[28] used in this case may be a companion for treatment of most cases of hypertension, even when the patients appear to be treatment-resistant.

The Impact of New Technology Like Home Blood Pressure Monitoring and Smartphone Apps on Blood Pressure Control

Professor Gianfranco Parati

A recent study has shown that only 13% of physicians are proactively utilising strategies to improve poor BP control, such as increasing dose and adding or switching to another drug.[30] Home BP monitoring with the use of new technologies, telemonitoring, and the recent progress in smartphone apps and patients' management software may help to improve BP control. Studies have shown that increases in home BP are more likely to predict increased risk of cardiovascular death compared with office BP,[31] while a recent meta-analysis has shown that home BP monitoring improves BP control.[32] In addition, the improved BP control achieved with home BP monitoring may be associated with improved patient adherence to treatment.[33]

It is often not possible to go through patient logs of BP values in detail during the short consultation times available. Telemonitoring may be a useful adjunct to home BP monitoring: data are collected, organised, analysed, and sent to the GP by email before each visit. The TeleBPCare study found that telemonitoring resulted in an important and significant increase in control of ambulatory BP compared with regular care, and also resulted in improved adherence.[34]

There are many smartphone apps available for healthcare, lifestyle, and wellbeing. Software is available to analyse the data on the physician's computer, in order to facilitate data interpretation and inform subsequent therapy decisions. The widespread availability of smartphones may provide potential for better care. There are a variety of different apps that permit measurement of HR, oxygenation, blood flow, and BP. However, few apps are validated and almost none are supported by the relevant scientific societies. Combining apps with a BP-monitoring device results in the formation of a medical device that requires legal regulation.[35]

The ESH has developed a specific, validated, and supported app for smartphones as part of the EUROHYPERTENSION project, with the aim of improving interaction between patients and physicians. This app allows collection of BP data and monitoring of changes over time, which can be easily sent directly to the patient's physician. In addition, users can obtain a simple summary of the ESH/ESC guidelines and information on hypertensive centres throughout Europe, thereby allowing the user to find and get in touch with experts for management of their hypertension. This app may be combined with the dedicated software that is in development for use by physicians to collect the data. This app may facilitate the achievement of BP control and a reduction in major cardiovascular risk factors, such as smoking, hypercholesterolaemia, and glycaemia.

In summary, the rate of BP control in Europe is still unacceptably low, especially considering the number of medications available and the progress in technology. Improvements in patient adherence to treatment and physician inertia to treatment intensification may help to improve BP control rates. It is important to consider the reasons behind patients' non-achievement of goals, e.g. due to side effects, difficulties in obtaining the prescription, and poor local healthcare system support, and therapies should be selected by matching with the individual patient's needs.Simplification of the therapeutic contact system is essential; single-pill

FDCs may help in improving adherence. Information technology has a role in improving BP control through better use of home BP monitoring with telemedicine and smartphone apps.

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