WHEN THE GOING GETS TOUGH, THE TOUGH GET GOING

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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]

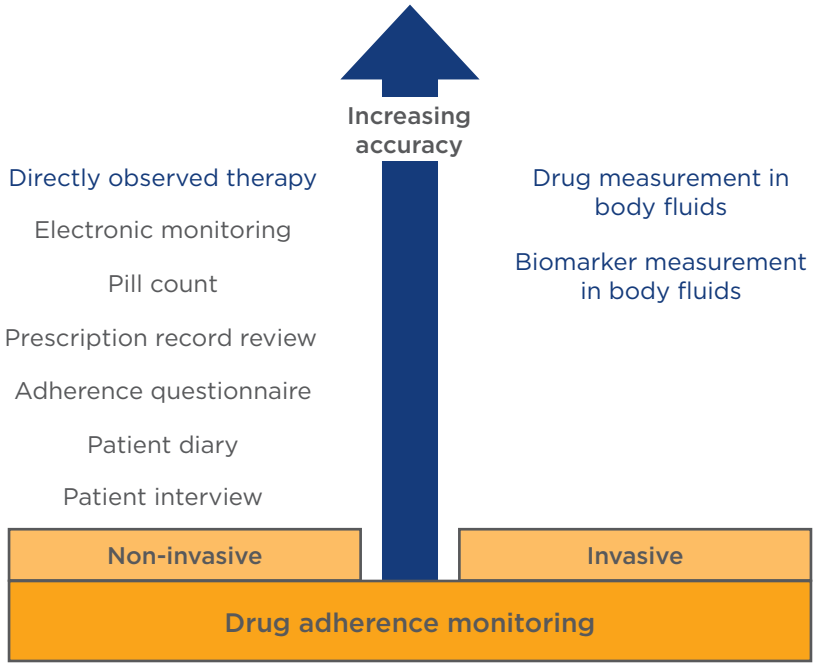

Figure 1: Long-term drug adherence is difficult to monitor.

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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