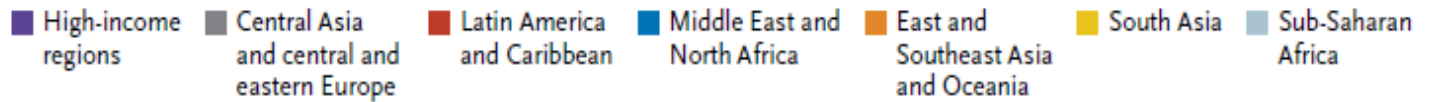


RESISTANT HYPERTENSION ..Reality or Illusion ?

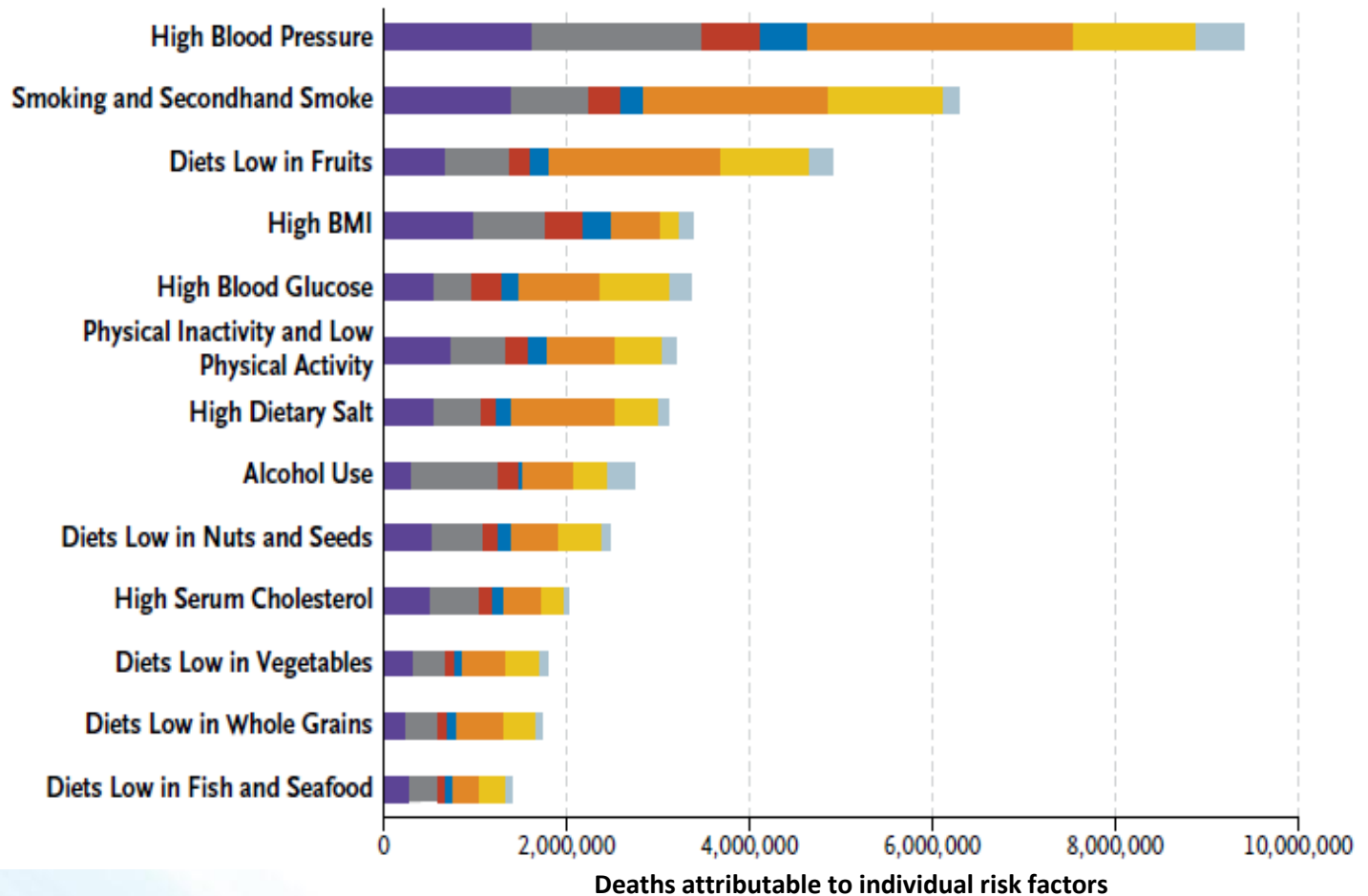
OSAMA OKKEH, MD,MRCP,PhD.(Cardiology)
Senior Consultant Interventional Cardiologist

Baghdad ,17 /11/ 2022...Iraq HTN Conference

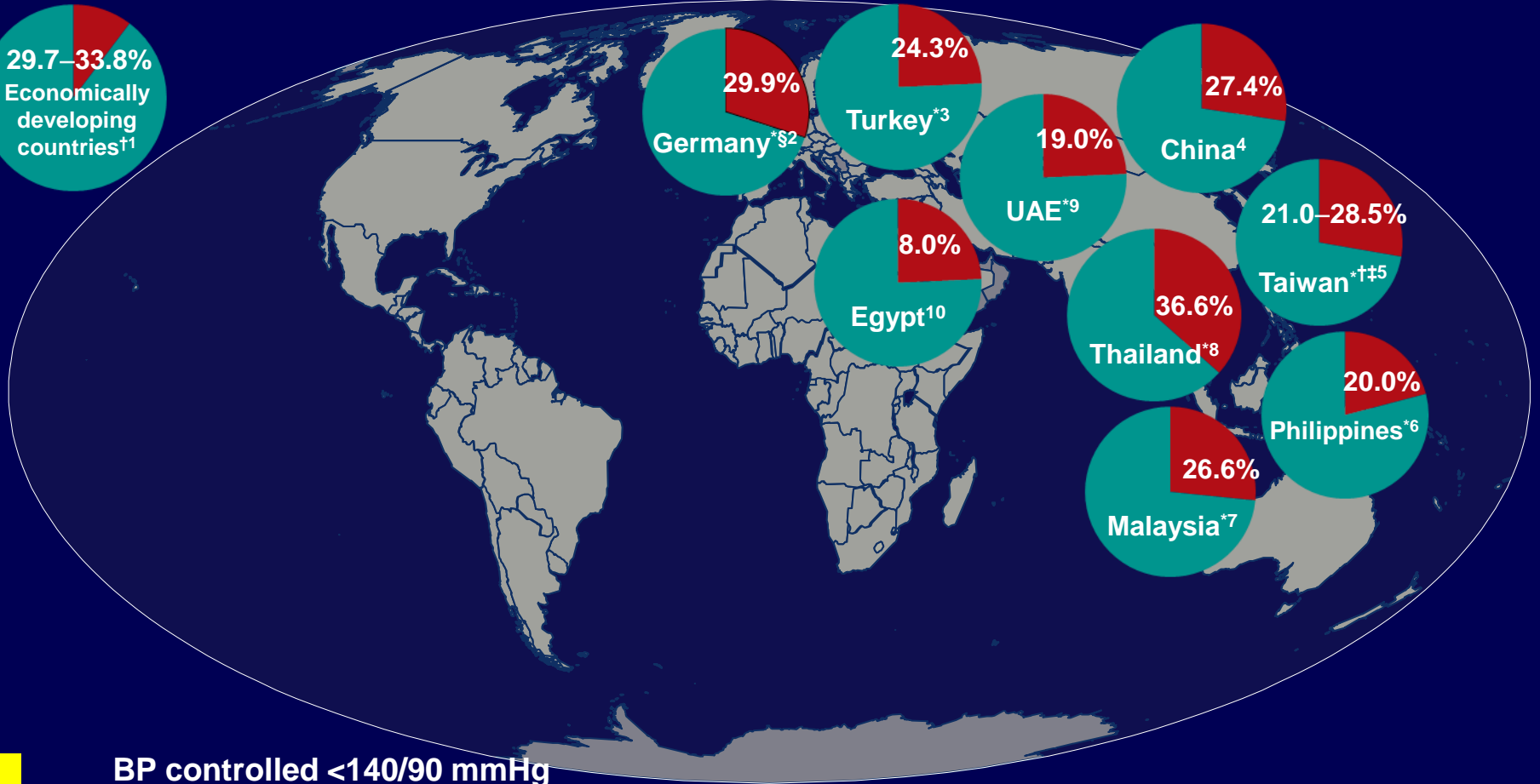
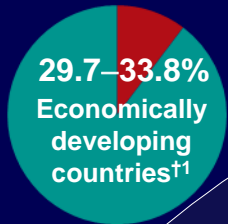
Hypertension is the leading cause of death globally, especially in Asia



A Deaths



‘Controlling blood pressure with medication is unquestionably one of the most cost-effective methods of reducing premature CV morbidity and mortality’



BP controlled <140/90 mmHg

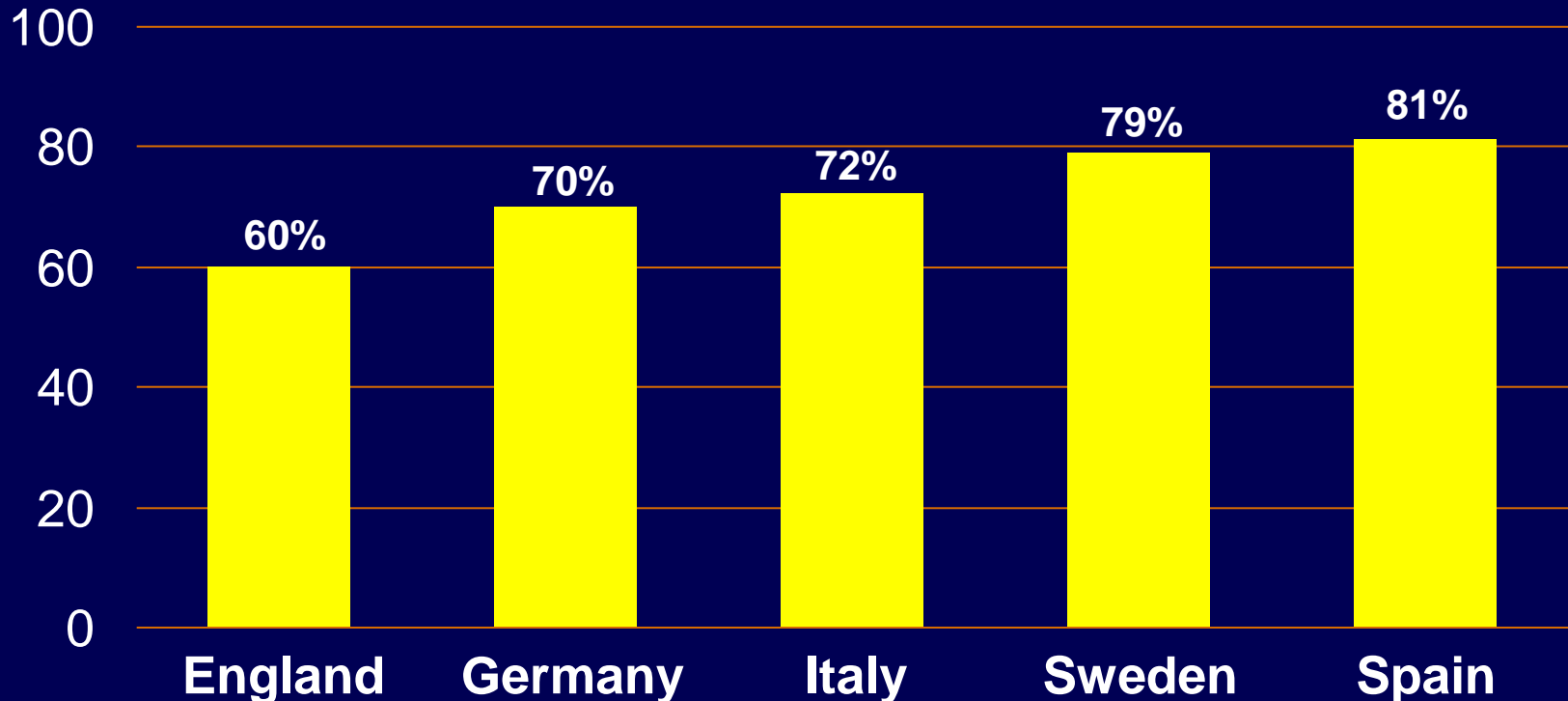
BP uncontrolled ≥140/90 mmHg

† Control rate shown in males % – females %; *Treated population;
 §patients age 35–64 years; ‡ adults aged ≥19 to 44 years; BP control levels not defined for China data

1. Pereira M et al. J Hypertens 2009; 27: 963–975; 2. Wolf-Maier et al. Hypertension 2004;43:10–17; 3. Erem et al. J Public Health 2009;31:47–58; 4. Wang et al. Chin J Epidemiol 2012;33:903–6; 5. Su et al. J Hypertens 2008;26:600–06; 6. Sison et al. PJC 2007;35:1–9; 7. Rampal et al. Public Health 2008;122:11–18; 8. Aekplakorn et al. J Hypertens 2008;26:191–8; 9. Ibrahim et al. Saudi J Kidney Dis Transplant 1999;10:376–81; 10. Ibrahim & Damasceno. Lancet 2012;380:611–19

Approximately 70% of Patients Who Receive Treatment for Hypertension Do Not Reach BP Goal in Europe

Patients not achieving BP goal (%)



BP goal is <140/90 mmHg

Wolf-Maier et al. Hypertension 2004;43:10–

- **Hypertension** remains
 - * **Inadequately diagnosed**
 - * **Inadequately treated**
 - * **Poorly controlled**

Classification of Office Blood Pressure

Table 3 Classification of office blood pressure^a and definitions of hypertension grade^b

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension ^b	≥140	and	<90

©ESC/ESH 2018

BP = blood pressure; SBP = systolic blood pressure.

^aBP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.

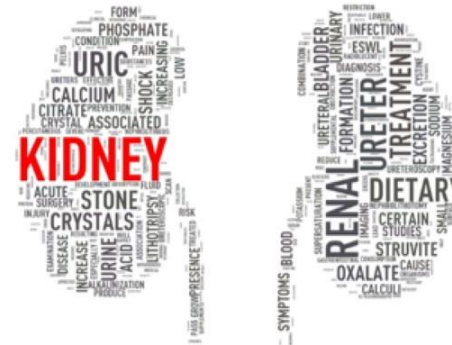
^bIsolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.

The same classification is used for all ages from 16 years.

Resistant hypertension treatment: current guidelines

Resistant HTN and Hard-to-Treat HTN

- **Resistant HTN** has been defined as BP above goal on ≥ 3 or controlled to goal on ≥ 4 BP medications prescribed at optimal doses^[a]
- But, in many instances, resistant HTN is an artifact of suboptimal regimens and/or patient non-adherence^[a]
- **Hard-to-treat HTN** may also describe the condition of elevated BP in patients with multiple comorbidities (eg, kidney disease)^[b]



a. Hwang AY, et al. *Hypertension*. 2016;68:1349-1354.
b. Saadat Z, et al. *Nephro Urol Mon*. 2015;7:e29863.

CV Risk Factors That May Complicate HTN Treatment

- Demographics
 - Male sex
 - Older age
 - Smoking
- Asymptomatic organ damage
 - Echocardiographic LVH
 - Carotid wall thickening or plaque
 - Ankle-brachial index <0.9
- Diabetes mellitus
- Established CV or renal disease

A systematic approach to management of treatment-resistant hypertension

Address Lifestyle Barriers to BP Control

```
graph TD; A[Address Lifestyle Barriers to BP Control] --> B[Address Usage of Interfering Substances]; B --> C[Address Adherence]; C --> D[Optimize Pharmacotherapy]; D --> E[Consider Referral to a Specialist];
```

Address Usage of Interfering Substances

Address Adherence

Optimize Pharmacotherapy

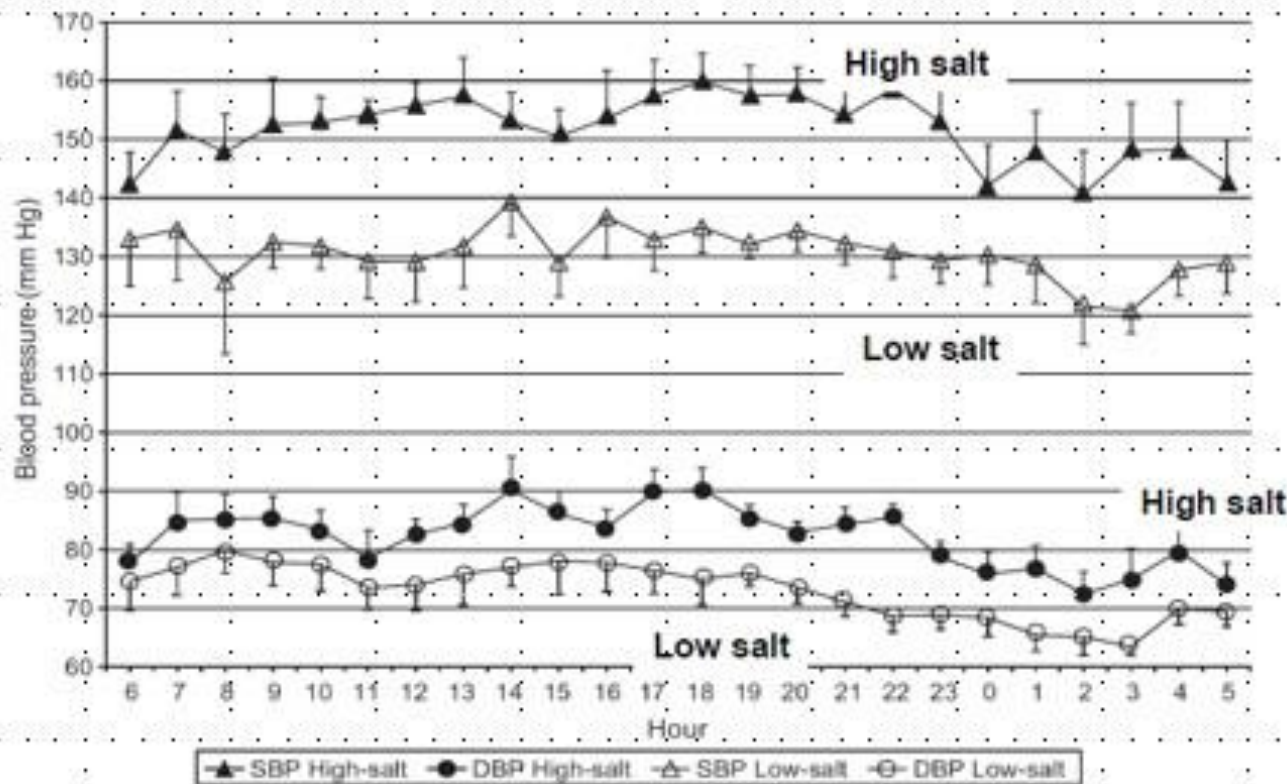
Consider Referral to a Specialist

Identify and reverse

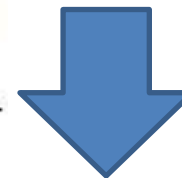
- High dietary salt intake
- Excessive alcohol consumption
- Obesity
- Sedentary lifestyle

Effects of Dietary Sodium Reduction on BP in Patients with Resistant Hypertension

7 days, randomized, cross-over, n=12, End-point 24h ABPM
Low sodium 50 mmol/24 h (U Na 46 mmol/24 h)
High sodium 250 mmol/24 h (U Na 252 mmol/24 h)



SBP
20.7
mmHg



DBP
9.6
mmHg

A systematic approach to management of treatment-resistant hypertension

Address Lifestyle Barriers to BP Control

Address Usage of Interfering Substances

Address Adherence

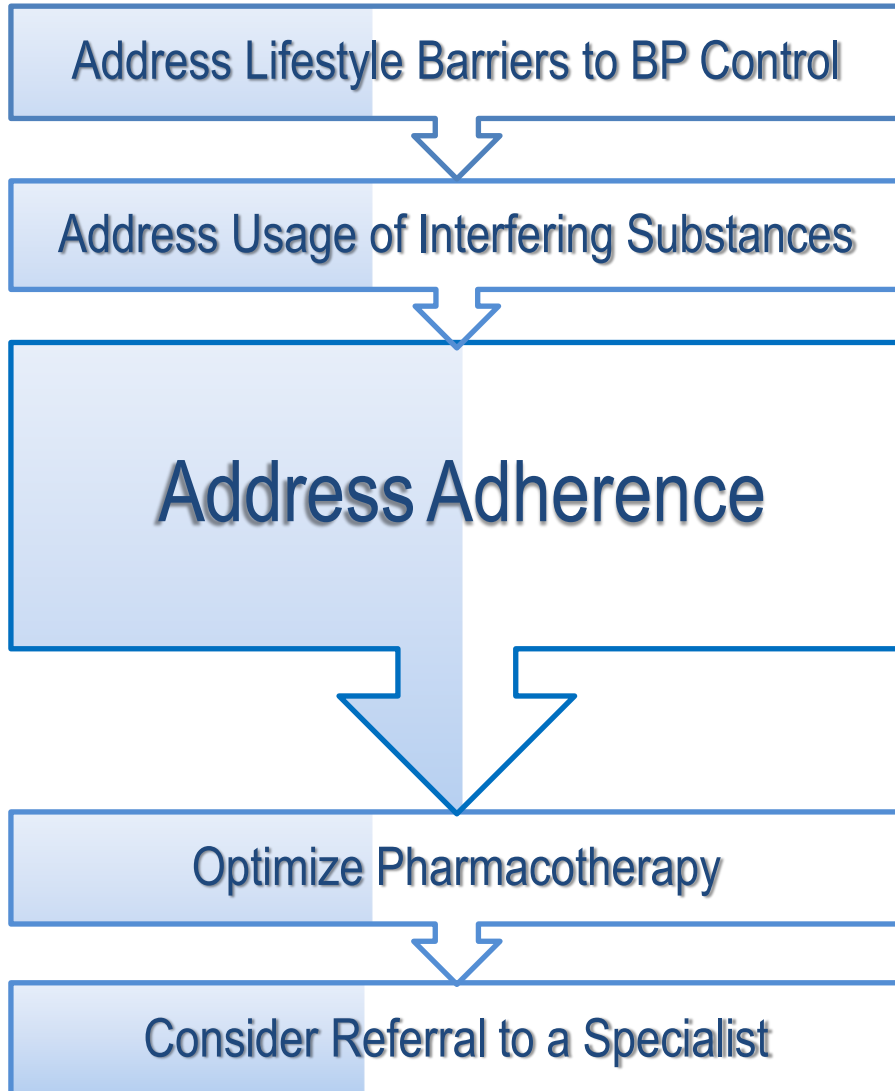
Optimize Pharmacotherapy

Consider Referral to a Specialist

Discontinue or minimize

- NSAIDs
- Sympathomimetic drugs
- Herbal supplements
- Anabolic steroids
- Appetite suppressants
- Erythropoietin
- Oral contraceptives

A systematic approach to management of treatment-resistant hypertension

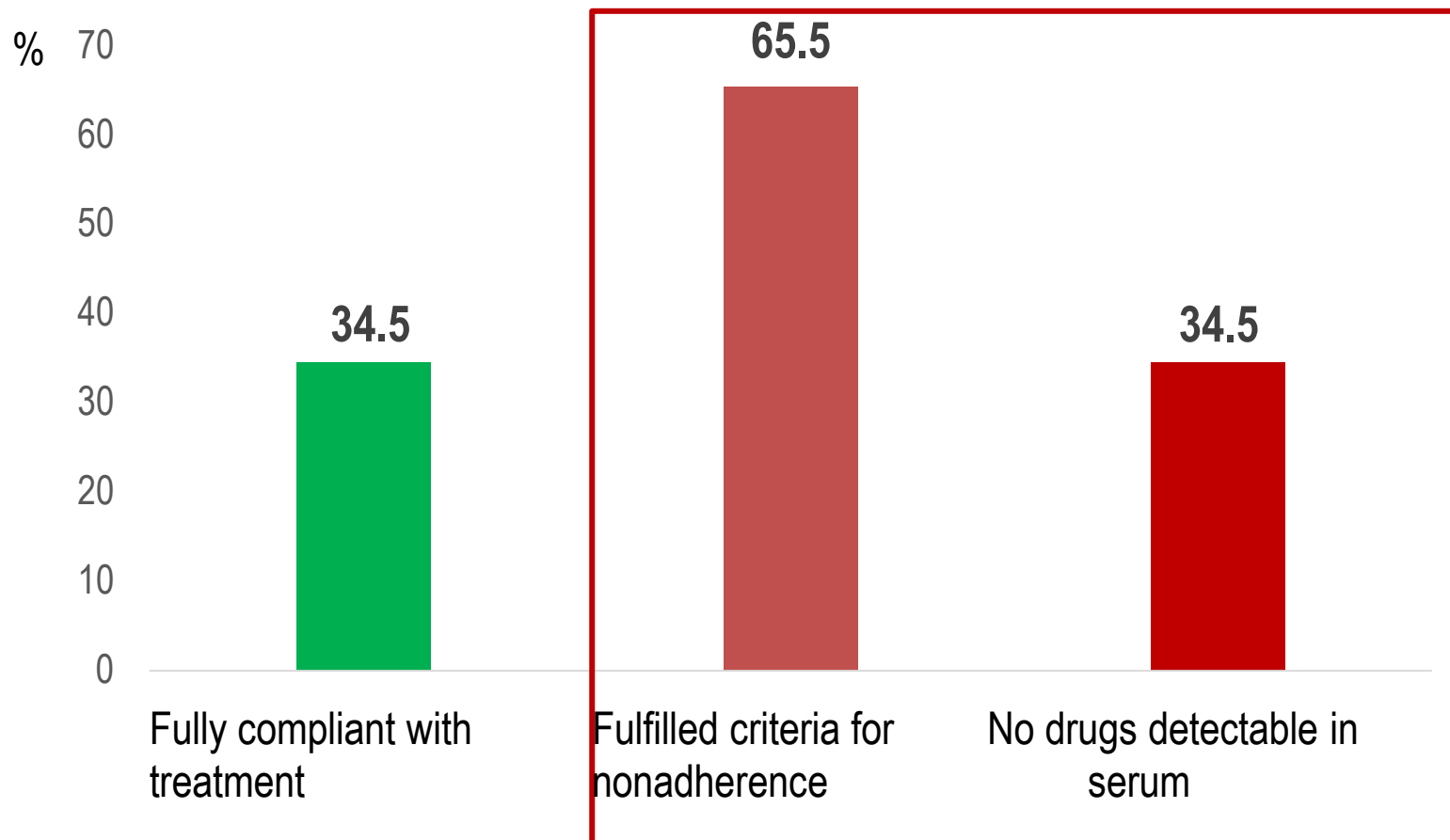


Is it resistant hypertension or resistant patient?

- Written patients reports
- Electronic pill boxes and pill counts
- **Therapeutic drug monitoring (TDM)**
- **Witnessed drug intake** (Directly observed therapy)

How Many Patients are Actually Adherent to Their Antihypertensive Medication?

A quantitative analysis based on serum drug levels in patients taking combination multidrug therapy, N=84, number of antihypertensives 5.0 ± 1.2



23% of Patients Referred for RND Do Not Take Drugs

208 pts in a Specialist Hypertension Centre, HP LC-MS/MS urine analysis

Non-adherence	New Referrals	Follow Up with nonadequate BPcontrol	Referred for RND
Complete	8.8%	9.1%	23.5%
Partial	9.6%	28.8%	-
Any	18.4%	37.9%	23.5%

Non-Adherence to Antihypertensive Agents: Results of a Urine-Based Assay

Measure of non-adherence	All	Group A	Group B	Group C
N	208	125	66	17
Complete non-adherence	21 (10.1)	11 (8.8)	6(9.1)	4 (23.5)
Partial non-adherence	31 (14.9)	12 (9.6)	19 (28.8)	–

Group A = new referrals from primary care; Group B = patients whose BP response to clinic-prescribed antihypertensive treatment was considered inadequate by a specialist; Group C = hypertensive patients formally referred for consideration of renal denervation. Average # of screened medications was 3 but 2 was the average number detected.

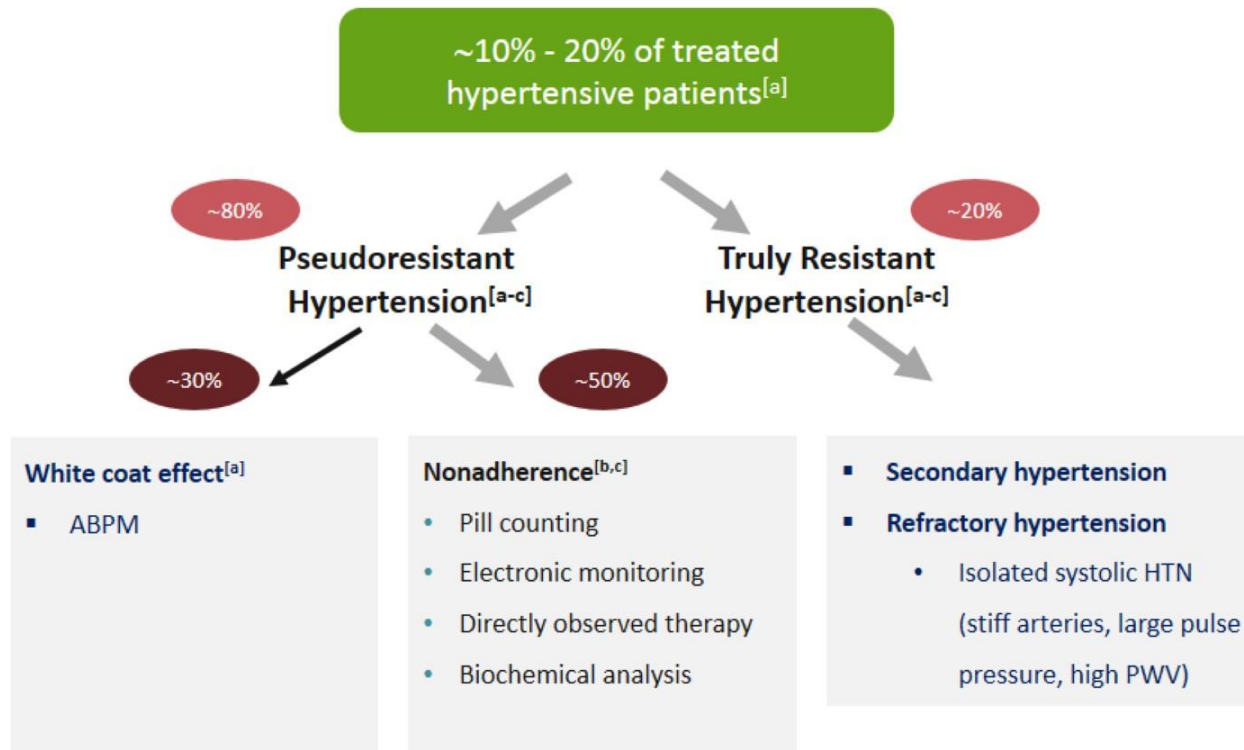
Data are presented as counts/percentages, medians with 25%-75% IQR or means and SDs

Urine assays designed to detect the presence of medications suggest that even patients who claim to be adherent may not be, particularly those on multi-drug regimens.

Tomaszewski M, et al. *Heart*. 2014;100:855-861.

(Apparent) Resistant HTN

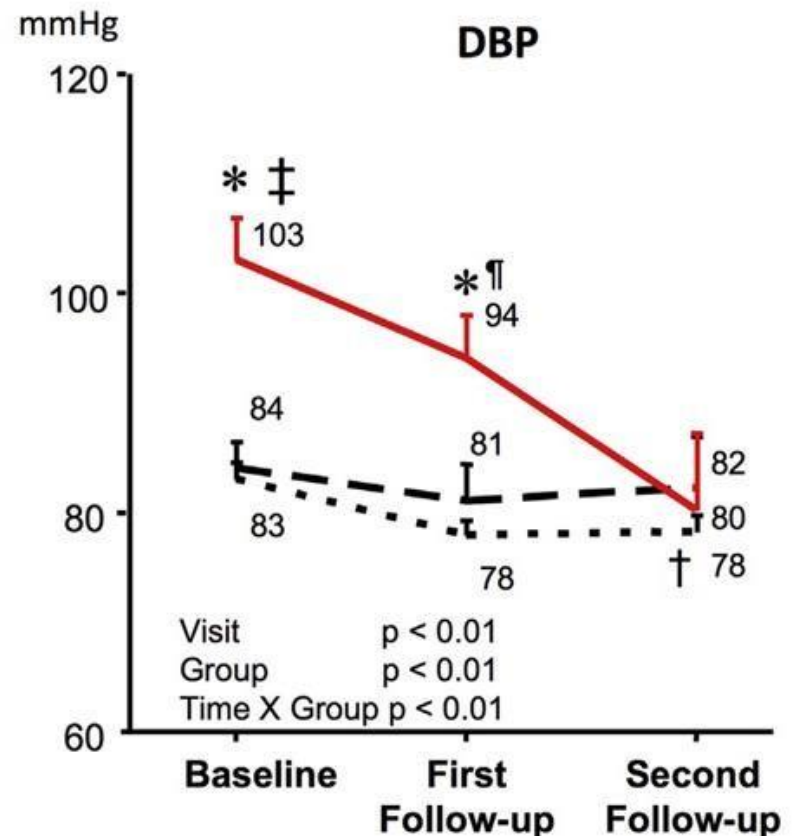
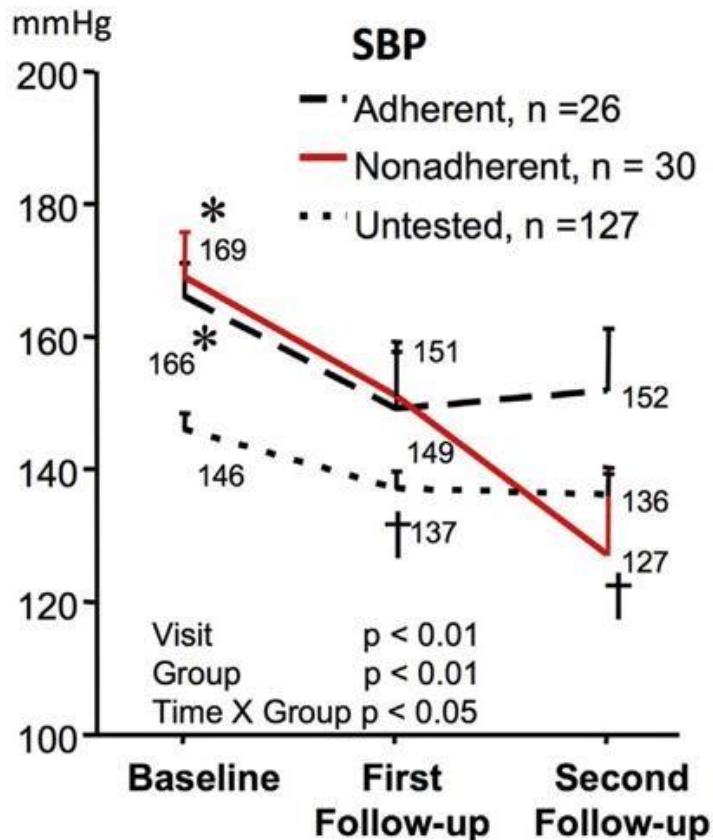
In Patients on Appropriate Triple Therapy



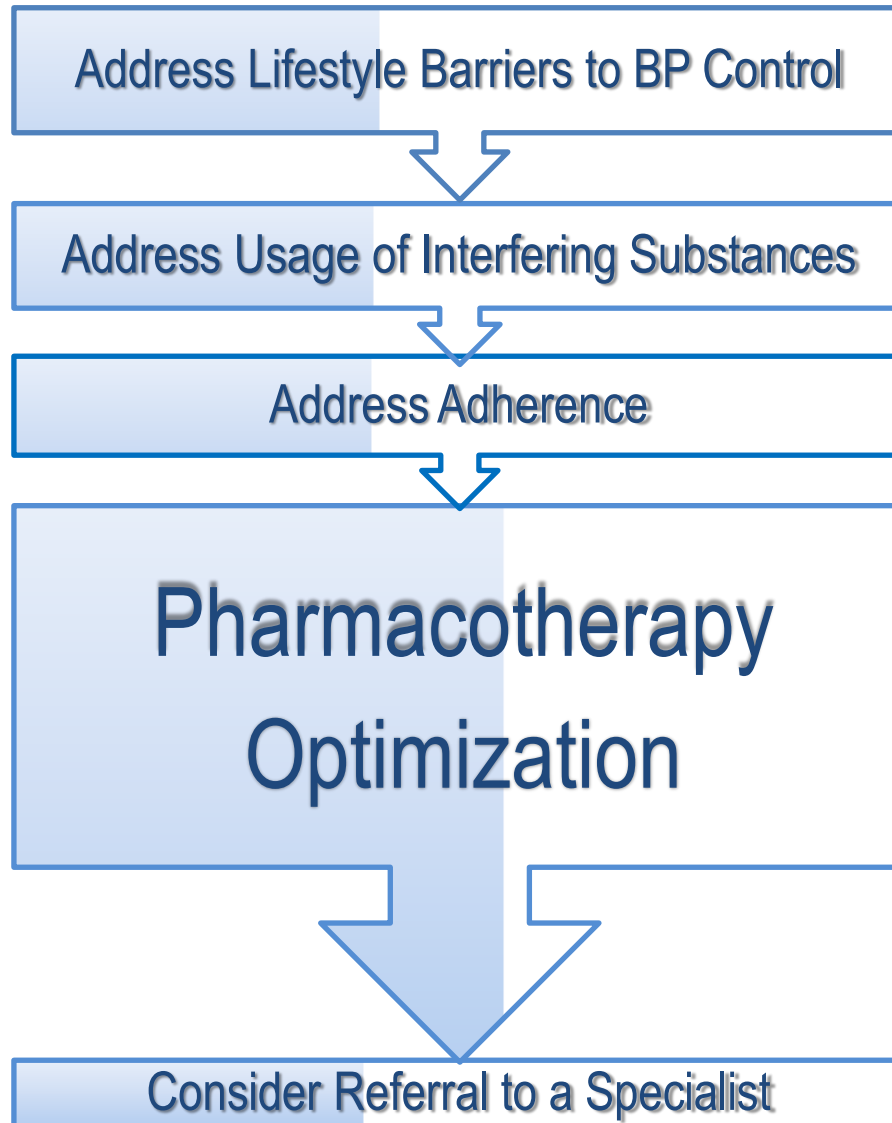
a. de la Sierra A, et al. *Hypertension*. 2011;57:898-902; b. Jung O, et al. *J Hypertens*. 2013;31:766-774; c. Burnier M, et al. *Semin Nephrol*. 2015;34:498-505.

Therapeutic Drug Monitoring Facilitates BP Control in Resistant Hypertension

N=56, all prescribed antihypertensive drugs were titrated to the maximal/ near-maximal doses
54% - nonadherent to treatment



A systematic approach to management of treatment-resistant hypertension



A common Cause of Resistant Hypertension

Diuretic/s deficiency



Not enough diuretic/ **Wrong** Diuretic

Current Dosages of Hydrochlorothiazide for HTN May Be Suboptimal

A meta-analysis of results from randomized clinical trials indicates that hydrochlorothiazide diuretics in its commonly used doses of 12.5 mg to 25 mg is clinically inferior in antihypertensive efficacy compared with other drug classes

Alternatively, the hydrochlorothiazide dose of 50 mg was associated with significant reduction in 24-hour systolic ambulatory BP

- However, the higher dose may be associated with metabolic side effects (loss of appetite, nausea, diarrhea)

But in combination with other HTN agents, the 25 mg dose may be safe and effective

Spironolactone as a 4th Drug Option: Background

Pathophysiological

- Secondary aldosteronism triggered by diuretic induced sodium depletion
- Aldosterone secretion escape associated with RAS blockade
- Relative hyperaldosteronism due to obesity¹

Clinical Trials

- ASCOT BPLA, 2007
- ASPIRANT, 2011
- PATHWAY-2, 2015

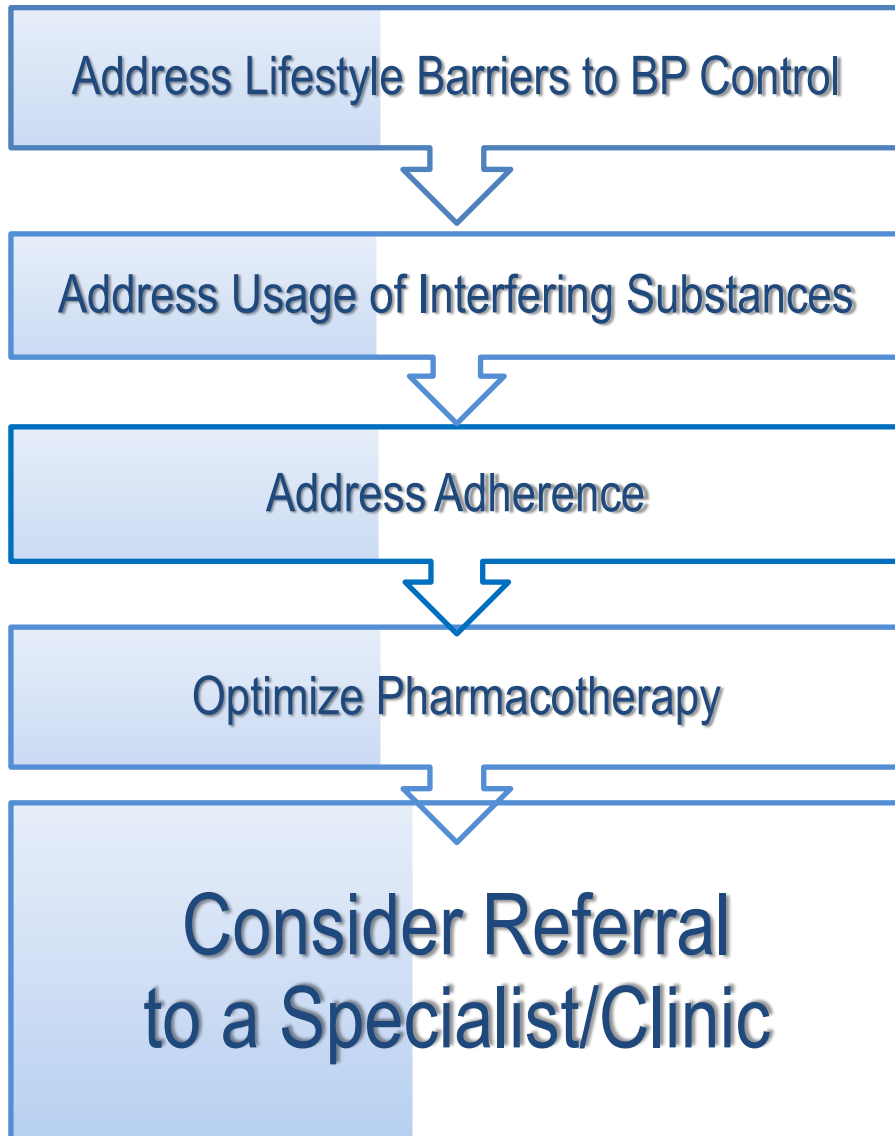
Chapman NC et al Hypertension. 2007; 49:839-845.
Vaclavík J et al Hypertension. 2011;57:1069-1075.
Williams B et al Lancet 2015; 386: 2059–68.

Practice Tips for Witnessed Drug Intake

«Physicians may have to consider **stopping** all current drugs and **restart** with a simpler treatment regimen under close medical supervision»

«A few days in **hospital** may be necessary to check the BP effect of antihypertensive drugs under strict control»

A systematic approach to management of treatment-resistant hypertension



Patients with TRH do benefit from referral to a hypertension specialist/clinic

- At 1-year follow-up patients achieved an 18/9 mmHg drop in BP, control rates increased from 18 to 52%¹
- 53% of patients were controlled to BP target (<140/90 mmHg)²

Selection for invasive treatment

Invasive Approaches in Patients with Resistant Hypertension

<p>In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered.</p>	IIb	C
<p>Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers.</p>	I	C
<p>It is recommended that the invasive approaches are considered only for truly resistant hypertensive patients, with clinic values ≥ 160 mmHg SBP or ≥ 110 mmHg DBP and with BP elevation confirmed by ABPM.</p>	I	C

CVD Risk Factors Common in Patients With Hypertension

Modifiable Risk Factors*	Relatively Fixed Risk Factors†
<ul style="list-style-type: none">• Current cigarette smoking, secondhand smoking• Diabetes mellitus• Dyslipidemia/hypercholesterolemia• Overweight/obesity• Physical inactivity/low fitness• Unhealthy diet	<ul style="list-style-type: none">• CKD• Family history• Increased age• Low socioeconomic/educational status• Male sex• Obstructive sleep apnea• Psychosocial stress

*Factors that can be changed and, if changed, may reduce CVD risk.

†Factors that are difficult to change (CKD, low socioeconomic/educational status, obstructive sleep apnea (12)), cannot be changed (family history, increased age, male sex), or, if changed through the use of current intervention techniques, may not reduce CVD risk (psychosocial stress) (12).

CKD indicates chronic kidney disease; and CVD, cardiovascular disease.



Non-Adherence and the Older Hypertensive Patient

Non-adherence to therapy is often presumed to be a problem with younger patients

However, findings from several recent studies suggest that non-adherence may also be problematic in older patients

- A study of older hypertensive patients (65 to 91 years) from that the frailty syndrome (presence of multiple comorbidities and deteriorated physical fitness) may exert a significant effect ($P < .001$) on treatment adherence^[a]
- Miller and colleagues' study of "baby boomers" and "seniors" with hypertension reported suboptimal rates of treatment adherence^[b]

a. Chudiak A, et al. *Clin Interv Aging*. 2017;12:805-814; b. Miller NH, et al. *J Clin Hypertens (Greenwich)*. 2010;12:328-334.

Improving Adherence to Therapy: Patient Communication Strategies

Don't ask your patients whether or not they are adherent to therapy

- They may become defensive and answer "of course" when "of course" is not correct

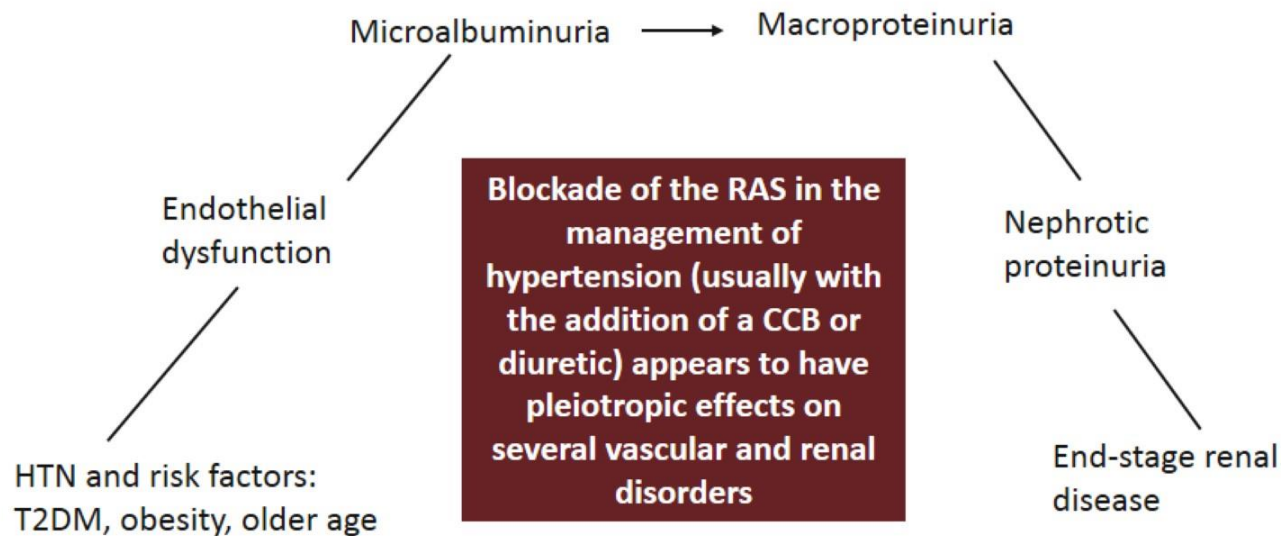
Ask instead "are there any days when you may not have taken your tablets?"

- The "softer" question may elicit a more truthful response

Take the time to explain to patients the importance of controlling BP

- Hypertension is largely asymptomatic; however, heart attacks and strokes are not

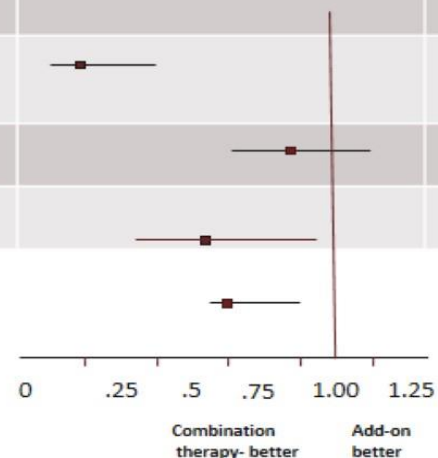
The Cardiovascular-Renal Continuum in The Context of Hypertension



Initial Combination HTN Therapy Reduces CV Event Rates

- The forest plot shows incidence rates and incidence rate ratios of CV events, initial combination vs add-on therapy

All Patients (1762 Patients in Each Cohort)	Incidence Rate* (Initial Combination Therapy vs. Add-on)	IRR (95% CI)†	Forest Plot	P Value†
Acute MI	0.45 vs 0.99	0.19 (0.10, 0.34)		<.0001
Stroke/TIA	2.57 vs 2.84	0.79 (0.59, 1.06)		.1172
HHF	0.55 vs 0.78	0.54 (0.31, 0.96)		.0311
Overall	3.34 vs 4.10	0.62 (0.48, 0.80)		.0002

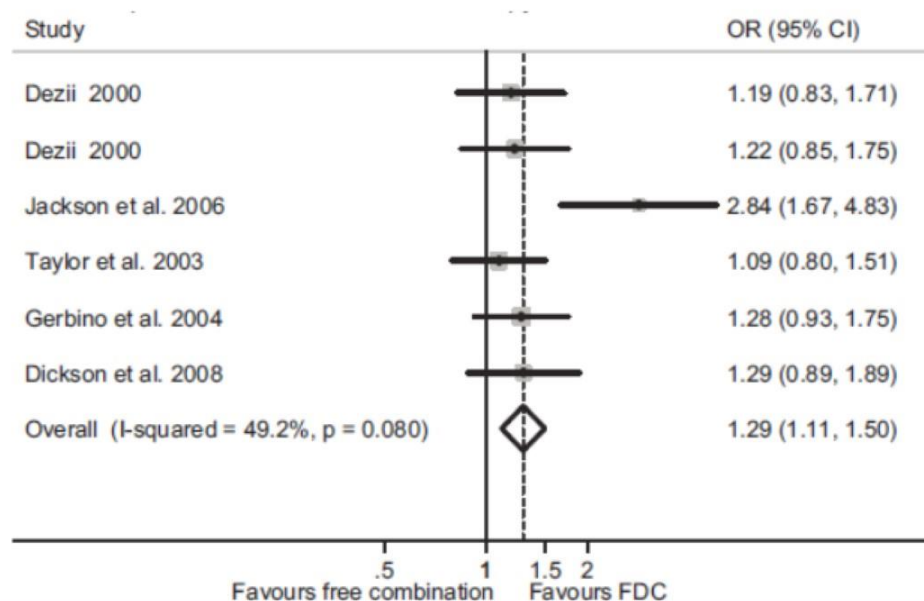


*Number of patients with an event per 100 person-year

† Statistical differences between exposure groups, as well as CIs, were calculated using conditional Poisson regressions adjusting to matched pairs

Gradman AH, et al. *Hypertension*. 2013;61:309-318.

Single-Pill Combinations vs Free Drug Components: Effects on Compliance

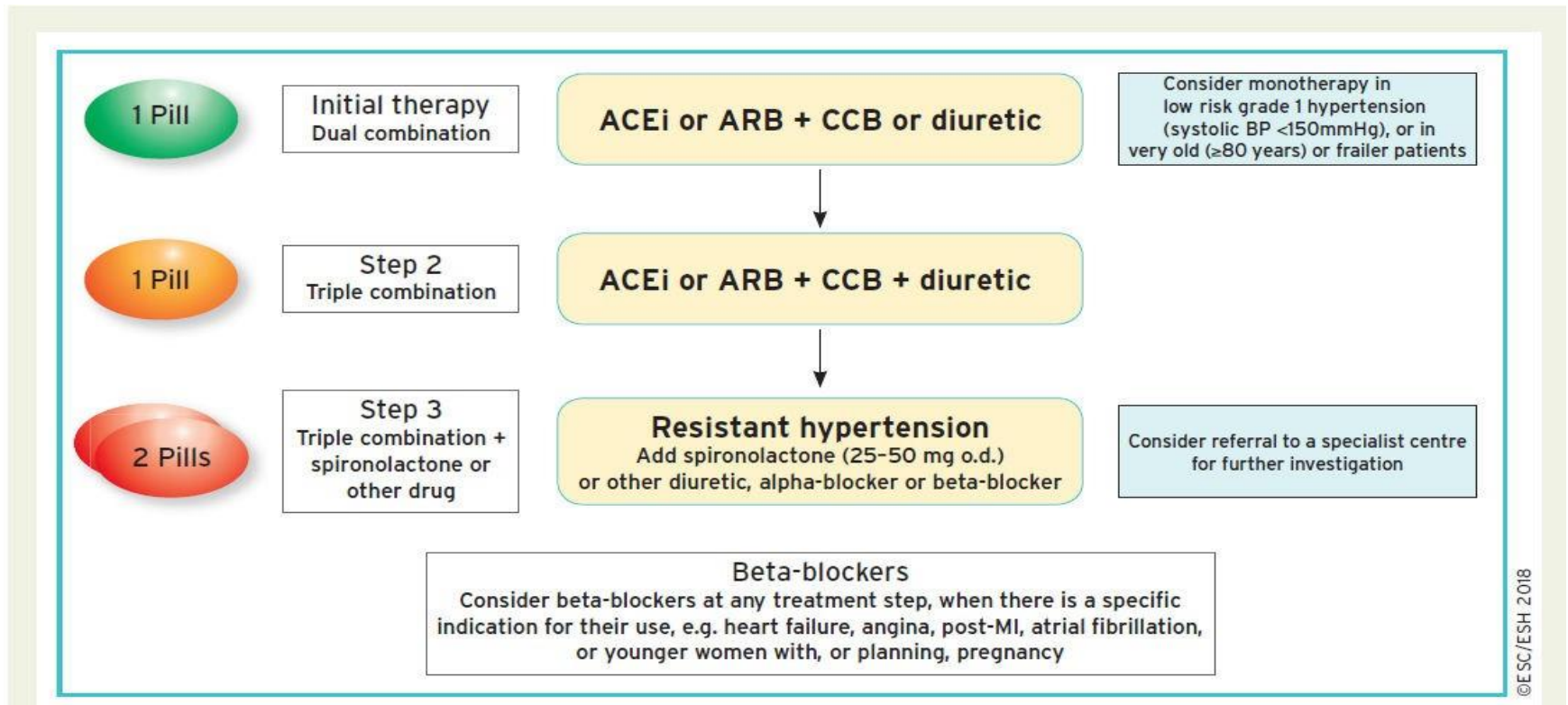


Analysis of the results of 6 retrospective studies, including data on 30 295 patients, showed that the use of an FDC as compared with the free-drug combination was associated with a 29% significant increase in compliance and persistence with therapy (OR: 1.29 [95% CI: 1.11 to 1.50])

Causes of Secondary Hypertension With Clinical Indications

Common causes
Renal parenchymal disease
Renovascular disease
Primary aldosteronism
Obstructive sleep apnea
Drug or alcohol induced
Uncommon causes
Pheochromocytoma/paraganglioma
Cushing's syndrome
Hypothyroidism
Hyperthyroidism
Aortic coarctation (undiagnosed or repaired)
Primary hyperparathyroidism
Congenital adrenal hyperplasia
Mineralocorticoid excess syndromes other than primary aldosteronism
Acromegaly

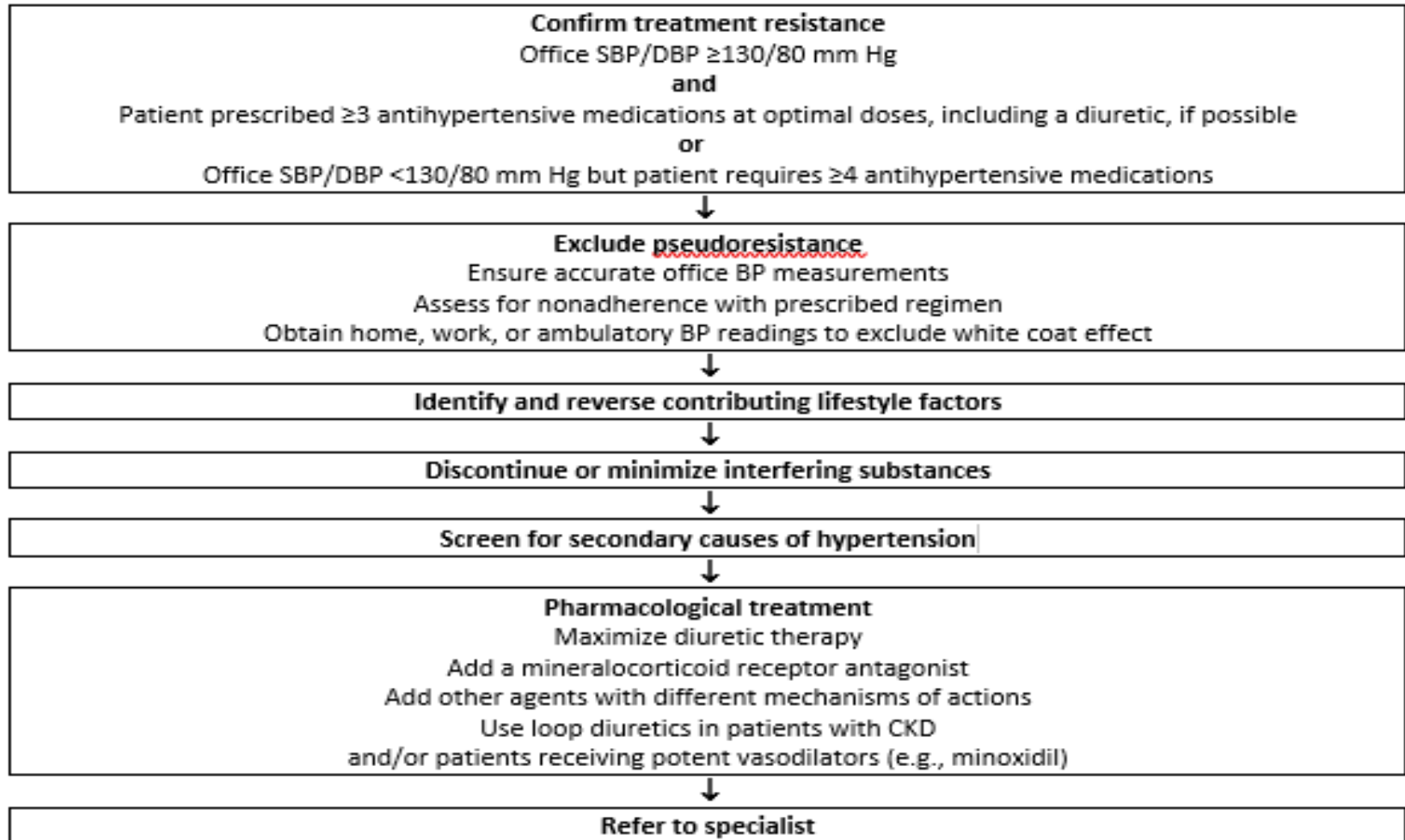
Drug Treatment Strategy For Hypertension and CKD



- **Absence of hypertension, overweight and smoking results in 9 disease-free years and prolonged life expectancy of 6 years**
-
- **Between 1989 and 2012, individuals ≥ 45 years from the Rotterdam Study were followed**
- **Conclusion**
- **This subanalysis of the Rotterdam Study showed that absence of the 3 common shared risk factors smoking, hypertension and overweight, results in 9 disease-free years and an increased life expectancy of 6 years compared to those with these 3 risk factors. These data emphasize that prevention of occurrence of smoking, hypertension and overweight may result in healthy aging and prevent premature death**

(Resistant !!) Hypertension: Diagnosis, Evaluation, and Treatment

Figure 10. Resistant Hypertension: Diagnosis, Evaluation, and Treatment



BP indicates blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; and SBP, systolic blood pressure.
Adapted with permission from Calhoun et al.

Summary and Conclusions

- Many patients with HTN have a complex form of the disease, wherein HTN is hard to treat, or complicated by a range of comorbidities
- Hard-to-treat HTN often appears to be incompletely responsive to multiple medications, but this failure of response is more often attributable to therapy non-adherence than to truly intractable disease
- Many clinical trials and observational studies have demonstrated that simplified treatment regimens, wherein single-dose combinations of 2 or even 3 agents are used, both improve adherence and do a significantly better job of reducing BP than do individual doses of the same medications

Thank You



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Senior Consultant Interventional Cardiologist