

# Recommendations for the treatment of hypertension in the elderly and very elderly – a scotoma within international guidelines

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## Summary

The recommendations of international scientific societies for the treatment of hypertension in the geriatric population are different. Lack of outcome trials, non-standardised terminology as well as differing levels of evidence contribute to the inconsistencies in the guidelines. This review article compares six international guidelines (ESH-ESC 2007/2009, SHG 2009, DHL 2008, CHEP 2010, NICE 2011 and JNC7 2003) as well as the consensus document of the ACCF/AHA 2011 in terms of their recommendations of drug classes, target blood pressure values and the use of combination therapy. Generally, antihypertensive therapy appears to be clinically beneficial in geriatric patients. Target blood pressure values of <140–150/90 mm Hg and <140/90 mm Hg can be used as a general guideline for octogenarians (80–89 yrs) and septuagenarians (70–79 yrs) respectively. While angiotensin-II converting enzyme inhibitors and diuretics appear to be advantageous in treating combined systolic-diastolic hypertension, calcium-channel blockers and diuretics are to be recommended in the management of isolated systolic hypertension. Combination therapy often increases the efficacy of the treatment as well as patient medication adherence. Furthermore, by making the most of drug combination synergy, lower doses may be used resulting in fewer side-effects.

**Key words:** hypertension; international guidelines; blood pressure; treatment; elderly

## Introduction

It is estimated that, by 2050, approximately a fifth of the global geriatric population will be 80 years or above [1]. Because the majority of these patients are diagnosed and treated in earlier life years, the cardiovascular sequelae are delayed until a greater age. Despite the increase of life ex-

pectancy within the last few decades and the significant increase in the size and proportion of geriatric patients, blood pressure (BP) control rates in old and very old patients remains low [2]. Up to 75% of this population does not meet target BPs. Inconsistencies within international guidelines appear to be generally underestimated, but may contribute to low BP control-rates in this particular populace. We have identified the following points as sources of conflicting opinion:

- Lack of information: Only a few scientific societies provide therapeutic recommendations for elderly patients. The rapid release of new data within the last few years is not yet reflected by all national societies, making such information inaccessible to health practitioners and patients alike.
- Lack of evidence: target BPs are not clearly defined and are mainly based on expert opinion.
- Varying level of evidence: There is disparity amongst different guidelines with regards to the level of evidence upon which recommendations are based.
- Non-standardised terminology: Almost all published guidelines, use different or novel terms for defining age ranges within the geriatric populace.
- Different approaches for the use of combined therapy: Therapy failure is often due to the apprehension of side effects and an increased pill burden which results in poor adherence in the elderly.

The aim of this review is to investigate six international guidelines with respect to their recommendations on target BPs, drug classes and combination therapy for old and very old patients and to highlight the current information in the Consensus Document of the American College of Cardiology Foundation / American Heart Association (ACCF / AHA 2011) [3].

## Selection of guidelines

Worldwide, there is in excess of 100 guidelines for the treatment of hypertension (HT). The inhabitants of Europe (739 million), the U.S. (310 million) and Canada (31 million) represent about one-seventh of the world's population [4] and have a high proportion of elderly patients. To represent these areas, we have chosen three continental-scope recommendations (European Society of Hypertension / ESH-ESC 2007 [5] and Reappraisal 2009 [6] for Europe, and the Canadian Hypertension Education Program / CHEP 2010 [7] as well as the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure JNC7 2003 [8] for North America). Due to existing differences within European health systems (National Health Service\*, model of social insurance\*\*, model of private insurance\*\*\*) we decided to compare the guidelines of the UK\* (National Institute for Health and Clinical Excellence / NICE 2011 [9], Germany\*\* (Deutsche Hochdruckliga [German Society of Hypertension] / DHL 2008 [10]) and Switzerland\*\*\* (Swiss Society of Hypertension/SHG 2007/2008 [11]).

## Treatment recommendations and target blood pressures

The concept of guidelines for the diagnosis and treatment of HT is a simple and pragmatic idea: BP thresholds are defined, where initiating pharmacological treatment and implementing lifestyle changes, have been proven to be clinically beneficial [3]. While target BPs can be easily specified in younger patients owing to the large number of relevant outcome studies, consistent and specific long-term outcome data are decidedly lacking for patients older than 79 years. An overview of selected outcome trials for patients in the elderly and very elderly is shown in table 1.

A crucial source of inconsistency in the limited available studies is the non-standardised terminology. For instance, whilst the terms “elderly” (“old”) and “very elderly” (“very old”) are widely used in the literature, their defined age ranges differ as per table 2. The ACCF / AHA 2011 [3] saw, for the first time, an attempt to stratify old age into “young old” (65–74 years), “older old” (75–84 years) and “old old” (85 years and above) [3]. This allowed for the application of definitive age-specific target BPs.

Further confounding the research is the entrenched concept of “long-term” studies as spanning at least four (4) years. In the case of the elderly, such spans are difficult to study, as the remaining life expectancy of old patients (8 years in 2002) may be less than this time period [12].

The evolution of guideline recommendations for the treatment of HT in the elderly saw a significant turning point with the publication of the Hypertension in the Very Elderly Trial (HYVET) [13]. HYVET was carried out primarily as a trial concerning the “old old” population and demonstrated a 30% reduction of stroke and a 23% reduction of cardiovascular morbidity and fatal events.

*Pre-HYVET:* Considering the limited number of patients >79 years who were included in trials, no conclusive statement about specific target BPs could be given. Up until 2007 it was even questionable whether treatment of hyper-

tension per se was beneficial in the very elderly [14]. Although it had been shown that a target BP <140/90 mm Hg significantly reduces cardiovascular risk in **middle-aged** patients, only one single study was conducted in **elderly** patients (65–85 years) applying this target and showed no clinical benefit [15]. In addition, no studies had ever been conducted on patients >79 years with stage I HT (140–159 mm Hg) [16].

Due to this lack of evidence, a “general” target BP recommendation for patients >80 years was lacking in the available guidelines or included within the recommendations for the population <65 years. For instance, a target BP of <140/90 mm Hg was maintained in the ESH-ESC 2007.

As a result, in a survey conducted in 2002 one quarter of doctors were of the opinion that the treatment of HT apportioned more risks than benefits to patients >85 years [17]. The same study also showed that approximately 65% of general practitioners were aware of a target systolic BP (SBP) of <140 mm Hg, yet 58% opted to initiate antihypertensive therapy only at a SBP >160 mm Hg [17].

*Post-HYVET:* Increasing evidence could be found of the impact of HYVET on guidelines. The ESH-ESC 2009 [6] recommends the HYVET target BP (SBP <150 mm Hg) in patients >80 years [8], citing potentially intolerable side-effects when aiming for a target BP of <140 mm Hg. Similarly, NICE 2011 [9] and DHL 2008 [10] recommend target BPs of <150/80 mm Hg in octogenarians. The SHG 2009 [11] favours a general target BP of <150/90 mm Hg, irrespective of whether a patient is “old” or “very old”. Different from this, CHEP 2010 [7] does not allude to a specific target BP. The ACCF / AHA 2011 [3] recommendation concerns a systolic target BP range of ≤140–150 mm Hg for patients >79 years depending on one or more criteria or contingencies (table 3).

### Is “lower” better?

Data from the Honolulu Heart Program suggest that excessive reduction of BP not only affects quality of life but can also increase cardiovascular risk [18]. A recent cohort study partly confirmed this in the elderly, demonstrating that both sustained, as well as regression of, DPB <70 mm Hg were independently associated with heart failure [34]. Thus, a significant increase in mortality has been shown in INVEST [19] when SBP or DBP drops below 115 mm Hg or 65 mm Hg respectively. Observational data indicate that the lowest target BP for attributable risk in septuagenarians is <135/75 mm Hg and <140/70 mm Hg for octogenarians [3].

However, the question remains whether certain co-morbidities (such as chronic renal disease, heart failure etc.) will benefit from more stringent target BPs. Neither the investigated guidelines nor the ACCF / AHA 2011 [3] take a clear stance on this. Despite existing expert opinion demanding that BP be lowered to <130/80 mm Hg in high-risk patients, there is currently little clinical evidence to support this. This question was raised within the Cardio-Sis study [20], which showed lower event rates in the “young old” with a systolic target BP of <130 mm Hg instead of <140 mm Hg. In contrast, the primary results of ACCORD [21] yielded no difference in event rates when a systolic target BP of <120 mm Hg or <140 mm Hg was applied.

Also, the assessment of cardiovascular risk by Framingham (and therefore the decision on how far the blood pressure should be lowered) is limited by its non-applicability to patients >70 years.

It is known that orthostatic hypotension (supine-to-standing BP drop of >20 or >10 mm Hg for SBP and DBP respectively) is known to occur more frequently (5–30%) in the elderly (patients >65 years) [33]. With regards to this condition the ESH-ESC 2009 [6] mentions an increased risk in the elderly on anti-HT therapy and advises routine standing BP measurements, but makes no treatment recommendations. Both DHL 2008 [10] and CHEP 2009 [7] recommend routine standing BP measurements and recommend that elderly patients should be tested for postural hypotension. Furthermore, DHL 2008 [10] emphasises lower initial drug doses in elderly patients. The JNC7 2003 [8] advises periodic standing BP measurements and mentions orthostatic hypotension as a potential complication of polypharmacy. Neither NICE 2011 [9] nor SHG 2009 [11] mention standing BP measuring or orthostatic hypotension.

Additionally, it should be addressed, that physicians have increasingly the responsibility to be the “manager” of death. This also refers to the establishment and expansion of antihypertensive therapy in situations of advanced malignant

diseases. An overview of the recommendations of the guidelines is shown in table 3.

## Drug recommendations

Although, unsurprisingly, significant BP reductions could be shown for all classes of drugs (in comparison to placebo), the efficacy differences appear to be marginal. Where, for instance, benefit has been shown for calcium channel blockers (CCB) and sartans (angiotensin-II receptor blocker, ARB) over beta blockers (BB) in LIFE [22] and SCOPE [23], the DHL 2008 [10], ESH-ESC 2007 [5] (and ESH-ESC 2009 [6]) and CHEP 2009 [7] do not express a preference for any specific drug classes on the basis of age. In contrast, the SHG 2009 [11] mentions the superior efficacy of diuretics (D) compared to BB. Therefore BB should not be used in the elderly [24], seeing as the results are not convincing for older patients [25]. In addition, a meta-analysis of 10 studies with BB and D in patients over 60 years showed that about 2/3 of the patients were well-controlled on D alone [26].

The ACCF/AHA 2011 [3] stresses, therefore, that initial therapy should, if possible be a D (hydrochlorothiazide [HCTZ], chlorthalidone, bendrofluzide) [3] and if another

**Table 1:** Summary of important outcome trials for patients in the elderly and very elderly.

Trial	Age of included patients (years)	N	Inclusion Criteria SBP / DBP (mm Hg)	Goal SBP / DBP (mm Hg)	Active Treatment	Control	BP Δ SBP / DBP (mm Hg)	Clinical benefit	Results
SHEP	≥60	4736	160–219 / <90	<160, ↓20	D BB	placebo	–12 / –4	+	↓ CV events (32%) ↓ stroke (36%) ↔ CV mortality
STOP (subgroup)	70–84	1627	≥180 / ≥90 OR DBP >105	<160 / <95	BB D	placebo	–19 SBP	+	↓ CV events (40%) ↓ stroke (46%) ↓ CV mortality (43%)
HYVET	≥80	3845	>160 / <110	<150 / <80	D ACEI	placebo	–15 / –6.1	+	↓ CV events (34%) ↓ stroke (30%) ↓ CV mortality (23%)
SYST.EUR	≥60	4695	160–219 / <95	SBD <150	CCB ACEI D	placebo	–10 / –5	+	↓ CV events (26%) ↓ stroke (42%) ↓ CV mortality (27%)
SCOPE	70–89	4937	160–179 / 90–99	<160 / 90	ARB	placebo	–4.7 / –2.6	+	↓ CV events (11%) ↓ stroke (24%) ↔ CV mortality
LIFE-ISH	55–80	1326	160–200 / <90	≤140 / 90	ARB	BB	–16,7 / –9.0	+	↓ CV events (27%) ↓ stroke (43%) ↓ CV mortality (47%)

SHEP Systolic Hypertension in the Elderly Program, STOP Swedish Trial in Old Patients with hypertension, HYVET HYpertension in the Very Elderly Trial, SYST.EUR SYSTolic hypertension in EUROpe trial, SCOPE The Study on Cognition and Prognosis in the Elderly, LIFE-ISH. The Losartan Intervention For Endpoint reduction in hypertension – Isolated Systolic Hypertension Subgroup, SBP systolic blood pressure, DBP diastolic blood pressure, D diuretic, BB beta-blocker, ACEI angiotensin converting enzyme inhibitor, ARB angiotensin-II receptor blocker, ↓ reduction in outcome, ↔ no difference in outcome

**Table 2:** Applied age definitions within investigated guidelines.

Age term	ESH-ESC 2007 [5] (years)	ESH-ESC 2009 [6] (years)	JNC7 2003 [8] (years)	CHEP 2010 [7] (years)	DHL 2008 [10] (years)	SHG 2009 [11] (years)	NICE 2011 [9] (years)	ACCF/AHA 2011 [3] (years)
Adults	–	<65	<65	<60	<60	–	<55	<65
Old (elderly)	–	65–79	65–x	60–x	60–79	–	65–79	65–74 (young old) 75–84 (older old)
Very old (very elderly)	≥80	≥80	–	≥80	≥80	–	≥80	≥85 (old old)

ESH-ESC 2007 Guidelines for the Management of Arterial Hypertension, ESH-ESC 2009 Reappraisal of European guidelines on hypertension management, JNC9 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, CHEP The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension, DHL 2008 Leitlinien zur Behandlung der arteriellen Hypertonie, SHG 2009 Schweizerische Hypertonie-Gesellschaft, NICE 2011 Clinical management of primary hypertension in adults, ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly

class were prescribed as first-line, the second drug should always be a D.

In a change from its previous version, NICE 2011 [9] recommended in 2011 initial treatment with a CCB or, if a CCB is unsuitable owing to e.g. oedema or intolerance, a “thiazide-like” D (indapamide / chlorthalidone) for all patients >55 yrs. This treatment recommendation remains unaffected even in the presence of ISH. If BP remains uncontrolled, either an ACE inhibitor (ACEI) or ARB is to be added as a second drug.

The JNC7 2003 [8] pursued a more rigid strategy, recommending that the treatment of older patients follow the same principles as for younger patients, regardless of the presence of a systolic-diastolic HT or ISH. Similar to the SHG 2009 [11], a BB should preferably be used for younger patients.

**Is there an “ideal combination”?**

HYVET saw the first data emerge regarding the use combined of D and ACEI therapy in old and very old patients.

An inhibitor of the renin-angiotensin-aldosterone system (RAAS) and a D – in particular HCTZ – have a synergistic pharmacological effect (inhibition of angiotensin-2-associated salt retention, vasoconstriction, and volume reduction). However, the use of HCTZ is limited in diabetics as thiazides reduce glucose tolerance. A clear superiority has been shown in ACCOMPLISH [27] for the combination of ACEI + CCB compared to ACEI + D (relative risk reduction of 21% for cardiovascular events). This effect was independent of age (either older or younger than 80 years). It is noteworthy that the superiority of the ACEI + CCB combination could not be explained by differences in BP. This result implies a possible class effect of antihypertensive drugs in certain populations, beyond the measurable therapeutic efficacy of these substances.

For the treatment of ISH, the ESH-ESC 2007 [5] recommends the use of CCB and D. While DHL 2008 [10] recommendations cite the results of underlying studies, the importance of initiating treatment with a CCB is stressed. Although CCBs have been proven to be successful in the

**Table 3:** Hypertension treatment recommendations for the elderly and very elderly according to investigated guidelines.

	Age	ESH-ESC 2007[5]	ESH-ESC 2009[6]	JNC7 2003[8]	CHEP 2010[7]	DHL 2008[10]	SHG 2009[11]	NICE 2011[9]
Recommended target BP (mmHg)	Old (elderly)	≤140/90						
	Very old (very elderly)	–	SBP ≤150 if ≥160 initially	≤140/90		≤150/80	–	≤150/90
Recommended substances	Old (elderly)	All (D, CCB, ARB, ACEI, BB)			All, no BB	All	All (esp. D) no BB	D, CCB
	Very old (very elderly)	–						D, CCB
Mentioned trials	Old (elderly)	SHEP, STOP, SYST.EUR, SCOPE, HYVET		–		LIVE SCOPE	–	–
	Very old (very elderly)	–	HYVET	–		HYVET	–	–
Is a treatment generally recommended?	Old (elderly)	Yes						
	Very old (very elderly)	Benefit remains unclear; cont. treatment if well tolerated	Depends on health condition; individualise treatment	–				yes
Recommendations for ISH (target BP in mm Hg)	Old (elderly)	D, CCB		–	D, ARB, CCB (≤140/90)	D, CCB, ARB	– (SBP ≤150)	D/CCB + ACEI/ARB (≤140/90)
	Very old (very elderly)	–						

**ACCF/AHA 2011[3]**

<p><b>Recommended target BP:</b>                  &lt;79 years: SBP &lt;140 mm Hg                  ≥80 years: SBP &lt;140–150 mm Hg                  (lower limit if SBD &lt;150 mm Hg can easily be attained with one or two drugs;                  higher limit if therapy regimen is complex, intolerable side effects, DBP drops &lt;65 mm Hg)</p>	<b>LVH</b>	<b>CAD</b>	<b>HF</b>	<b>CVD</b>	<b>CKD</b>
	ACEI, ARB	BB, CCB possible reduced EF: ACEI ACS: BB, ACEI	D, BB, ACEI, aldosterone –AAG; if ACEI is not tolerated: ARB	D + ACEI	ARB, ACEI if non-diabetic nephropathy: ACEI if proteinuria: ARB
	<b>PVD</b>	<b>DM</b>	<b>MS</b>	<b>Uncomplicated HT</b>	
	ACEI or ARB + BB	ACEI or ARB	–	Thiazide-D, CCB, ACEI, ARB, BB	

ESH-ESC 2007 Guidelines for the Management of Arterial Hypertension, ESH-ESC 2009 Reappraisal of European guidelines on hypertension management, JNC9 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, CHEP The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension, DHL 2008 Leitlinien zur Behandlung der arteriellen Hypertonie, SHG 2009 Schweizerische Hypertonie-Gesellschaft, NICE 2011 Clinical management of primary hypertension in adults, ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly, target BP target blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure, D diuretic, CCB calcium channel blocker, ARB angiotensin-II receptor blocker, ACEI angiotensin-II converting enzyme inhibitor, BB beta-blocker, LVH left ventricular hypertrophy, CAD coronary artery disease, HF heart failure, CVD cerebrovascular disease, CKD chronic kidney disease, EF ejection fraction, ACS acute coronary syndrome, PVD peripheral vascular disease, DM diabetes mellitus, MS metabolic syndrome, HT hypertension

treatment of ISH, the potential for dose escalation is limited due to the relatively common side effect peripheral oedema [28]. New studies show that the combination of HCTZ with an ACEI or ARB may reduce the incidence of oedema [28]. CHEP 2010 [7] expands upon the recommendation of initial treatment with D and CCB by specifying ARB as an alternative. The ACCF / AHA 2011 [3] indirectly address the treatment of ISH with their treatment recommendations for “complicated” hypertension (table 3). The SHG 2009 [11] and JNC7 2003 [8] guidelines contain no recommendation for the treatment of ISH (table 3).

### Combination therapies in elderly patients

The right choice of drugs and application modes have an influence on efficacy and tolerability [29]. As a result the establishment of therapy is often associated with a subjective decrease in quality of life, owing to an increased pill burden and adverse drug reactions. Adding insult to injury, elevated BP in the geriatric population is often asymptomatic, even in the presence of end-organ damage or serious comorbidities and the perceived low “benefit-to-risk ratio” is unacceptable to patients.

Polypharmacy is a particularly unfortunate reason for poor adherence [30] and high discontinuation rate, as it not only increase the responder rates by up to 70% [31] but may also reduce side-effects by neutralising counter-regulatory mechanisms [32]. The increased pill burden of polypharmacy may be circumvented by single-pill combinations, which also have the added benefit of component synergism, requiring lower individual drug dosages and lowering the occurrence of side-effects.

Severe, mono-therapy resistant HT is common in the old and very old and in most cases this necessitates the use of combination therapy. The rationale for this therapeutic approach is reinforced by the fact that additional end-organ damage or comorbidities are common in this population.

The use of combination therapies in older patients is explicitly recommended in ESH-ESC 2007 [5] and in DHL 2008 [10]. Initial combination therapy is especially attractive in patients with high cardiovascular risk [14] and should be initiated for BP-to-target BP differences  $\geq 20/10$  mm Hg [10]. This opinion is also shared by ACCF / AHA 2011 [3] and CHEP 2010 [7]. Although the 2009 ESC-ESH Reappraisal, as well as NICE 2011 [9] advocate gradual dose titration (up to maximum dose), both guidelines discuss the advantage of single-pill combinations. Differing from this, the ACCF / AHA 2011 [3] allows the use of an additional drug, even if the maximum dose for the initial drug has not been reached yet.

#### Are combined therapies always beneficial?

Despite the therapeutic benefit of combination therapy and increased compliance of single pill combinations in old and very old patients, their use is not without risks. Therefore, the use of combination products as first-line treatment (regardless of the degree of hypertension) is not generally recommended. It must not be forgotten that BP can drop substantially in elderly patients with a primary initiation of a combination therapy. Since up to 18% of octogenarians

show an impairment of cortical function or dementia, a lack of adherence to a single-pill combination must be taken more seriously, as an omission of combined (and often long-acting) substances often lead to loss of BP control.

### Concluding remarks

The investigated global guidelines differ in their treatment and target BP recommendations. These differences are due to the relatively immature field of study, which has seen development only in the last five years, but also by the different levels of underlying evidence. As a result, national and international societies deal with this topic with varying approaches. This may lead to uncertainty amongst both general practitioners and specialists [3]. Whilst the DHL 2008 [10] provides extended information, the comments of SHG 2009 [11] and JNC7 2003 [8] are marginal. The ACCF / AHA 2011 [3], an “expert consensus”, represents the first document that provides detailed information on data development within the past eight years. However, several unresolved issues still remain and need to be clarified in the future:

- Continuation of the development of the new definitions “young old”, “older old” and “old old”. Even though the ACCF / AHA 2011 mentions this new terminology it still refers to “patients  $\leq 79$  years” and “patients  $> 79$  years” (i.e., with 80 years being the cut-off between the two groups). This terminology must be clarified.
- High-level evidence such as RCTs regarding the benefits for different target BPs ( $<150$  vs.  $<140$  mm Hg) are lacking and should be conducted.
- It is recommended that geriatric subgroups demonstrating atypical clinical responses to pharmacotherapy (i.e. patients in whom drugs have higher/lower efficacy) be identified.
- It is still unclear to what degree BP goals need to be adapted in old and very old patients with additional risk factors and/or end-organ damage.

Because of the incomplete evidence, currently no recommendation can be made for the treatment of HT in the elderly and very elderly with absolute confidence. However, the following principles may be taken as general guidelines:

1. Older patients benefit equally to younger patients from antihypertensive treatment.
2. Target blood pressures:
  - For octogenarians ( $>80$  years) – a target BP of  **$<140-150/90$  mm Hg** should be applied to regardless of additional risk factors.
    - The ideal target BP is  **$<140/90$  mm Hg** and should be attempted if BP control (SBP  $<150$  mmHg) can be accomplished by the use of by one or two drugs.
    - Alternatively, if a) more than three drugs are necessary, b) unacceptable side effects occur or c) treatment hypotension develops (DBP drops below 65 mmHg), a target BP of  **$<150/90$  mm Hg** is acceptable.

- For septuagenarians (>70 years) and patients as young as 65 years – a target BP of <140/90 mm Hg is appropriate.
- 3. Drug choices
  - There is some evidence for the greater efficacy of **ACEI + D** for combined systolic/diastolic HT.
  - **D** should, whenever possible, be part of the therapy.
  - **CCB and D** should be used in patients with ISH.
  - Combination therapy, especially single-pill combinations, should be considered as it is effective in reducing side effects and in increasing efficacy and patient adherence.

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