New Guidelines for Hypertension With Comorbidities

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This session focused on the latest guidelines for the treatment of hypertension in patients with dyslipidemia, diabetes, atrial fibrillation (AF), and chronic kidney disease (CKD).

2013 AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION GUIDELINES ON THE TREATMENT OF BLOOD CHOLESTEROL

Genovefa Kolovou, PhD, Onassis Cardiac Surgery Center, Athens, Greece, provided an overview of the American College of Cardiology/American Heart Association 2013 guidelines on the treatment of blood cholesterol [Stone NJ et al. *Circulation* 2013], highlighting changes in the recommendations since the previous version.

Dr. Kolovou stressed that these guidelines address treatments proved to reduce atherosclerotic cardiovascular disease (ASCVD) events and are not intended to be a comprehensive approach to lipid management. The updates in the new guidelines focus on identifying individuals most likely to benefit from statin therapy and clarify treatment goals for lowering low-density lipoprotein cholesterol (Table 1).

Table 1. ACC/AHA 2013 Guideline Updatesa

ASCVD risk reduction 4 statin benefit groups	Individuals most likely to benefit from statin therapy: ▪ Clinical ASCVD ▪ Primary elevation of LDL-C to >190 mg/dL ▪ Diabetes without ASCVD, aged 40–70 years, LDL-C 70–190 mg/dL ▪ No ASCVD or diabetes, LDL-C 70–189 mg/dL, ASCVD 10-year risk >7.5%
Statin therapy	High-, moderate-, and low-intensity statins for use in secondary and primary prevention identified
Treatment goals	▪ ASCVD events are reduced by maximal tolerated statin dose ▪ No evidence to support the use of specific LDL-C treatment targets ▪ Nonstatin therapies do not provide acceptable ASCVD risk reduction compared with potential for adverse effects
Risk assessment	▪ Recommends using the new pooled cohort equations to estimate 10-year ASCVD risk ▪ Equations identify higher risk individuals most likely to benefit from therapy
Safety	Characteristics predisposing individuals to statin adverse effects: ▪ Multiple or serious comorbidities ▪ History of statin intolerance or muscle disorders ▪ Unexplained ALT elevation >3 times ULN ▪ Concomitant use of drugs that affect statin metabolism ▪ Age >75 years
Biomarkers and noninvasive tests	Additional factors to consider in select patients not in 1 of the 4 statin benefit groups: ▪ Primary LDL-C ≥160 mg/dL ▪ Family history of premature ASCVD with onset <55 years in first-degree male relative or <65 years in first-degree female relative ▪ hsCRP >2 mg/L ▪ CAC score ≥300 Agatston units ▪ Ankle-brachial index <0.9 ▪ Increased lifetime risk for ASCVD

ALT=alanine aminotransferase; ASCVD=atherosclerotic cardiovascular disease; CAC=coronary artery calcium; hsCRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; ULN=upper limit of normal.

Adapted from Stone NJ et al. *Circulation* 2013.

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The new guidelines identify high-, moderate-, and low-intensity statins for use in the secondary and the primary prevention of ASCVD (Table 2).

Table 2. High-, Moderate-, and Low-Intensity Statin Therapy[a]

High Intensity	Moderate Intensity	Low Intensity
Daily dose lowers LDL-C on average by about ≥50%	Daily dose lowers LDL-C on average by about 30%–50%	Daily dose lowers LDL-C on average by <30%
Atorvastatin (40[b])–80 mg Rosuvastatin 20 (*40*) mg	Atorvastatin 10 (*20*) mg Rosuvastatin (*5*) 10 mg Simvastatin 20–40 mg[c] Pravastatin 40 (*80*) mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* Pravastatin 10–20 mg Lovastatin 20 mg *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

LDL-C=low-density lipoprotein cholesterol.

[a]Adapted from Stone NJ et al. *Circulation* 2013. Statins and doses in italics are approved by the US Food and Drug Administration but were not tested in the reviewed randomized clinical trials (RCTs).

[b]Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg.

[c]Initiation of simvastatin 80 mg or titration to 80 mg not recommended by the Food and Drug Administration because of increased risk for myopathy, including rhabdomyolysis.

Dr. Kolovou concluded that ASCVD is the most important public health problem of our time. Achieving consistency of clinical care, incorporating new evidence, and its synthesis into practical recommendations for clinicians is the task of various guideline committees throughout the world. According to Dr. Kolovou, the guidelines could be enhanced by refining the use of lipid goals rather than by removing them.

HYPERTENSION MANAGEMENT AND GLYCEMIC CONTROL IN DIABETES

Peter M. Nillson, MD, PhD, Skane University Hospital, Malmo, Sweden, discussed guidelines for blood pressure (BP) and glycemic control in patients with diabetes. The goals of antihypertensive therapy in patients with diabetes are to lower BP and reduce cardiovascular risk and mortality.

Both the European guidelines on cardiovascular disease prevention [Perk J et al. *Eur Heart J* 2012] and the American Diabetes Association (ADA) Standards of Medical Care in Diabetes 2014 [ADA. *Diabetes Care* 2014] recommend a hypertension treatment target in patients with diabetes of <140/80 mm Hg. The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) recommendations [Mancia et al. *Eur Heart J* 2013] are shown in Table 3.

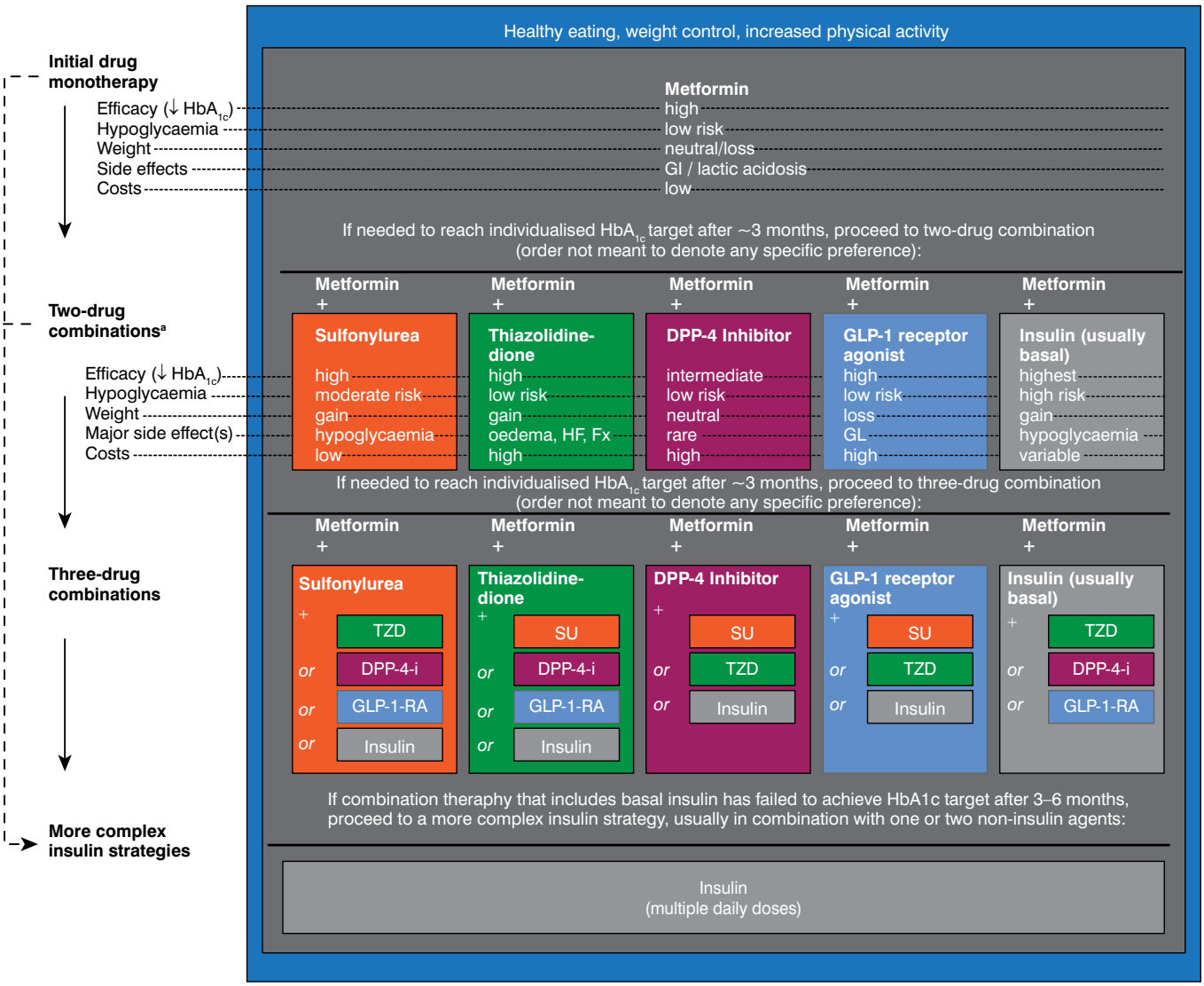
Table 3. ESH/ESC Guidelines for the Treatment of Hypertension in Diabetes and Metabolic Syndrome

Recommendation	Class	Level
Diabetes		
Treatment initiation mandatory for patients with SBP ≥160 mm Hg; treatment strongly recommended for SBP ≥140 mm Hg	I	A
SBP goal <140 mm Hg recommended	I	A
DBP goal <85 mm Hg recommended	I	A
All classes of antihypertensive medications recommended; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria	I	A
Individual drug choice should take comorbidities into account	I	C
Simultaneous administration of 2 RAS blockers not recommended and should be avoided	III	B
Metabolic syndrome		
Weight loss and exercise are recommended	I	B
Antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, are preferred	IIa	C
Prescribe antihypertensive medications with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mm Hg after suitable period of lifestyle changes, and maintain BP <140/90 mm Hg	I	A
BP-lowering drugs not recommended in individuals with metabolic syndrome and high normal BP	III	A

BP=blood pressure; DBP=diastolic blood pressure; RAS=renin-angiotensin system; SBP=systolic blood pressure.

The ESC/European Association for the Study of Diabetes and ESH/ESC guidelines both suggest that combination therapy is often necessary for patients with diabetes and hypertension. When combination therapy is needed, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), calcium antagonist, and thiazide diuretic are recommended. The guideline cautions against using an ACE inhibitor plus an ARB or a direct renin inhibitor because of the adverse effects of acute kidney injury and hyperkalemia. Beta-blockers should be used in patients with concomitant symptomatic coronary heart disease. Thiazides and beta-blockers may increase the risk for new-onset diabetes.

Figure 1. ADA/EASD Guidelines for Glycemic Control in Patients With Type 2 Diabetes



ADA=American Diabetes Association; DPP=dipeptidyl peptidase; EASD=European Association for the Study of Diabetes; GI=gastrointestinal; GLP=glucagon-like peptide; HbA1C= glycated hemoglobin; SU=sulfonylurea; TZD=thiazolidinedione.

Reproduced with permission from Springer Verlag from Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;55(6):1577–1596.

The ADA/European Association for the Study of Diabetes (EASD) 2012 guidelines for glycemic control [Inzucchi SE et al. *Diabetologia* 2012] in patients with diabetes recommend initial drug monotherapy with metformin in addition to lifestyle changes. More advanced regimens should use multiple glucose-lowering drugs, possibly insulin (including greater than once daily injections; Figure 1). Glycated hemoglobin (HbA1C) targets may need to be adjusted to avoid hypoglycemia.

Flexible goals for controlling hypertension (<140/85 mm Hg) and hyperglycemia (<7% HbA1C) are now recommended to avoid adverse effects, especially in the frail elderly (<8%–9% HbA1C). The ADA's BP goal for patients with diabetes, now <140/80 mm Hg, has gradually changed to become more like the European goal. The ESH/ESC and ESC/EASD 2013 guidelines both recommend a BP goal of <140/85 mm Hg, but the International Society of Hypertension/American Society of Hypertension recommend a goal of <140/90 mm Hg.

THERAPY FOR PATIENTS WITH ATRIAL FIBRILLATION AND HYPERTENSION

Patients with hypertension have an increased risk for AF, which leads to reduced cardiac function and increased risk for thromboembolism. Enrico Agabiti Rosei, MD, University of Brescia, Italy, discussed the various guidelines for antihypertensive, antiarrhythmic, and antithrombotic therapy for patients with AF.

The 2013 ESH/ESC guidelines for the management of arterial hypertension recommend considering treatment with an ARB, an ACE inhibitor, a beta-blocker, or a mineralocorticoid receptor antagonist to prevent AF and a beta-blocker or nondihydropyridine calcium antagonist for ventricular rate control in hypertensive patients with AF [Mancia et al. *Eur Heart J* 2013]. The 2012 focused update of the ESC guidelines [Camm AJ et al. *Eur Heart J* 2012] recommends antiarrhythmic therapy according to underlying pathology. Patients with AF have a nearly 5-fold increased risk for stroke [Wolf PA et al. *Stroke* 1991]. A meta-analysis found that two-thirds of strokes due to AF are preventable with appropriate anticoagulant therapy; in 29 trials of 28,044 patients, adjusted-dose warfarin reduced ischemic stroke by 67% and all-cause mortality by 26% [Hart RG et al. *Ann Intern Med* 2007]. The new oral anticoagulants (NOACs), dabigatran, rivaroxaban, apixaban, and edoxaban have been evaluated for stroke prevention in several trials. A meta-analysis of randomized clinical trials comparing NOACs with warfarin reported a 19% overall reduction in stroke risk and a 14% overall reduction in major bleeding risk with NOACs versus warfarin [Ruff CT et al. *Lancet* 2014].

The ESC AF 2012 [Camm AJ et al. *Eur Heart J* 2012] and AHA/ACC/Heart Rhythm Society 2014 [January CT et al. *Circulation* 2014] guidelines for the treatment of AF recommend warfarin, dabigatran, rivaroxaban, or apixaban in patients with CHA_2DS_2VASc scores ≥2. The American College of Chest Physicians 2012 guidelines [Guyatt GH et al. *Chest* 2012] recommend dabigatran 150 mg twice daily rather than vitamin K antagonist therapy, while the Canadian Cardiovascular Society AF guidelines [Skanes AC et al. *Can J Cardiol* 2012] recommend dabigatran, rivaroxaban, or apixaban over warfarin (Table 4).

According to Prof. Agabiti Rosei, prevention of AF and new treatment regimens are needed, considering the increasing elderly population, high percentage of uncontrolled hypertension, risk for stroke, and worsening of other comorbidities. Management of AF includes antihypertensive, antiarrhythmic, and antithrombotic drugs.

Table 4. US, European, and Canadian Guidelines for the Management of Patients With Atrial Hypertension

Recommendation	COR	LOE
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended; options include		
Warfarin	I	A
Dabigatran, rivaroxaban, or apixaban	I	B
With warfarin, determine INR at least weekly during initiation and monthly when stable	I	A
Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR	I	C
American College of Chest Physicians 2012 guidelines (ninth edition)		
2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation, we suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist therapy.		
Focused 2012 update of the Canadian Cardiovascular Society AF guidelines:		
We suggest that, when OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban[a] in preference to warfarin.	Conditional recommendation, high-quality evidence	

AF=atrial fibrillation; COR=class of recommendation; INR=international normalized ratio; LOE=level of evidence; OAC=oral anticoagulant; TIA=transient ischemic attack.

[a]Once approved by Health Canada.

Table 5. Hypertension Treatment for Patients With Nephropathy

Recommendation	Additional Considerations
Consider lowering SBP to <140 mm Hg	
Consider SBP <130 mm Hg with overt proteinuria	Monitor changes in eGFR
RAS blockers more effective to reduce albuminuria than other agents	Indicated in presence of microalbuminuria or overt proteinuria
Combination therapy usually required to reach BP goals	Combine RAS blockers with other agents
Combination of 2 RAS blockers	*Not recommended*
Aldosterone antagonist *not recommended in patients with CKD*	Especially in combination with a RAS blocker Risk for excessive reduction in renal function, hyperkalemia*

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; RAS=renin-angiotensin system; SBP=systolic blood pressure.

*On November 21, 2014, this row was moved from the Recommendation column to the Additional Considerations column.

Prof. Agabiti Rosei also emphasized that most patients with hypertension and AF do not control BP adequately, and this might represent a risk for cerebral hemorrhage, particularly during anticoagulant therapy.

TREATMENT OF HYPERTENSION IN PATIENTS WITH KIDNEY DISEASE

The latest guidelines for the treatment of hypertension in patients with CKD were discussed by Demetrios V. Vlahakos, MD, Attikon University Hospital, Athens, Greece. According to the 2013 ESH/ESC guidelines for the management of arterial hypertension, patients with CKD and hypertension have a high to very high risk for cardiovascular disease [Mancia et al. *Eur Heart J* 2013]. For patients with CKD stage 3 or ≥4, the guidelines recommend lifestyle changes for those with high normal BP (systolic BP [SBP] 130–139 mm Hg or diastolic BP [DBP] 85–89 mm Hg) and lifestyle changes plus antihypertensive therapy targeting a BP <140/90 mm Hg for patients with hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg).

A meta-analysis studying the effects of intensive BP lowering on the progression of kidney disease reported that intensive BP therapy improved outcomes and reduced the risk for end-stage kidney disease [Lv J et al. *CMAJ* 2013]. Subgroup analysis showed that intensive BP lowering reduced the risk for kidney failure for patients with baseline proteinuria but not for those without proteinuria.

BP-lowering therapies recommended by the 2013 ESH/ESC guidelines are shown in Table 5.

The 2014 evidence-based guideline for the management of high blood pressure in adults recommends that antihypertensive therapy in adults with CKD include an ACE inhibitor or ARB to improve kidney outcomes [James PA et al. *JAMA* 2014].

Prof. Vlahakos concluded that guidelines provide evidence-based recommendations for the thresholds, goals, and drug treatment strategies for the management of hypertension. However, guidelines are not a substitute for clinical judgment, and decisions must carefully consider the specific characteristics of each patient.