당뇨병 치료의 최신 경향

(Traditional Glucose-centric to the New Cardiorenal-metabolic Approach for the Treatment of Type 2 Diabetes)

April 14, 2023 Jiyun Park, MD. PhD

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Agenda

- 환자 특성에 따른 혈당 조절 목표
- 당뇨병 약제 선택
- 당뇨병 환자의 혈압 및 LDL 콜레스테롤 조절

Glucose-lowering studies confirmed benefit on microvascular complications but mixed results on macrovascular outcomes NIDDM

Study	Baseline HbA1c (%)	Control vs intensive HbA1c at study end (%)	Mean duration of diabetes at baseline (years)	Micro- vascular		CV di	sease	Mortality		
UKPDS ^{1,2}	7.1 (mean)	7.9 vs 7.0	Newly diagnosed	\downarrow	↓	\leftrightarrow	↓	\leftrightarrow	↓	
ACCORD ^{3,4}	8.1 (median)	7.5 vs 6.4	10.0	↓*		\longleftrightarrow		1		
ADVANCE ^{5,6}	7.5 (mean)	7.3 vs 6.5	8.0	\downarrow	↔ †	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	
VADT ⁷	9.4 (mean)	8.4 vs 6.9	11.5	\downarrow	?	\leftrightarrow	↓	\leftrightarrow	\leftrightarrow	
Kumamoto ⁸	9.0 (mean)	9.4 vs 7.1	6/10	\downarrow						

Long-term follow-up

Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology.

^{*}No change in primary microvascular composite but significant decreases in micro-/macroalbuminuria; †No change in major clinical microvascular events but significant reduction in ESKD (p=0.007)

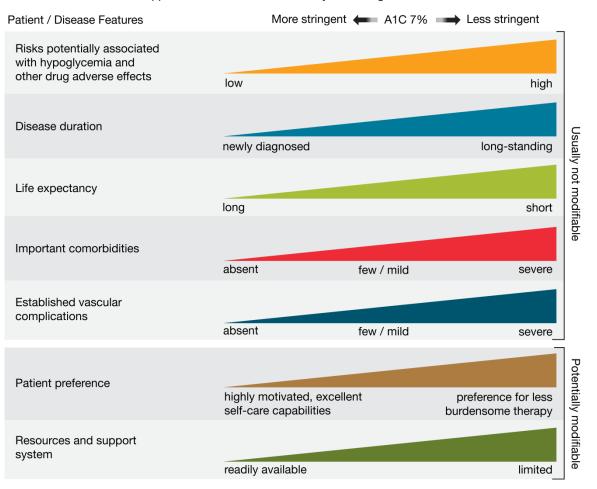
^{1.} UKPDS Group. Lancet 1998;352:837. 2. Holman RR et al. N Engl J Med 2008;359:1577. 3. Genuth S & Ismail-Beigi F. Clin Endocrinol Metab 2012;97:41.

^{4.} Ismail-Beigi F et al. Lancet 2010;376:419. 5. Patel A et al. N Engl J Med 2008;358:2560.

^{6.} Zoungas S et al. N Engl J Med 2014;371:1392. 7. Hayward RA, et al. N Engl J Med 2015;372:2197. 8 Diabetes Res Clin Pract. 1995 May;28(2):103-17.

환자 특성에 따른 혈당 조절 목표

- KDA: < 6.5% for T2DM adults, < 7.0% for T1DM adults
- ADA: < 7.0% for T1&T2DM adults, periprandial glucose 80-130mg/dL, peak postprandial glucose<180mg/dL



Approach to Individualization of Glycemic Targets

 고령, 긴 당뇨병 유병기간, 진행된 심혈관 질환 동반, 짧은 기대여명, 중증 저혈당의 위험에 따라 혈당 조절 목표를 높이 설정

환자 특성에 따른 혈당 조절 목표

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0-7.5% (53-58 mmol/mol)	80-130 mg/dL (4.4-7.2 mmol/L)	80-180 mg/dL (4.4-10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or two or more instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate- to-severe cognitive impairment or two or more ADL impairments)	Limited remaining life expectancy makes benefit uncertain	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<140/90 mmHg	Consider likelihood of benefit with statin

This table represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living; LTC, long-term care. ‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. "Multiple" means at least three, but many patients may have five or more (66). **The presence of a single end-stage chronic illness, such as stage 3—4 heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. Adapted from Kirkman et al. (3).

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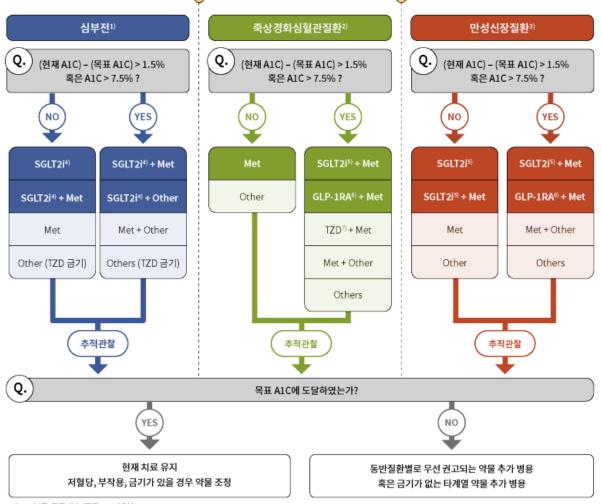
Algorithm 1 | 당뇨병 치료 시작

생활습관교정 교육 및 모니터링 Q. Algorithm 3 심각한 고혈당 (A1C > 9.0%)과 함께 고혈당으로 인한 YES)= 주사제 중 인슐린 증상 (다음, 다뇨, 체중 감소 등)이 동반되어 있는가? Q. Algorithm 4 기저 질환으로 심부전이, 죽상경화심혈관질환이 혹은 YES) 만성신장질환책이 동반되어 있는가? 동반질환 Q. Algorithm 2 (현재 A1C) - (목표 A1C) > 1.5%? 혹은 A1C > 7.5% ? 병용요법 Metformin 조기병용요법 (Algorithm 2 참조) Other 추적관찰 Q. 목표 A1C에 도달하였는가? YES 현재 치료 유지

저혈당, 부작용, 금기가 있을 경우 약물 조정

Algorithm 4 | 동반질환

생활습관교정 유지 및 모니터링



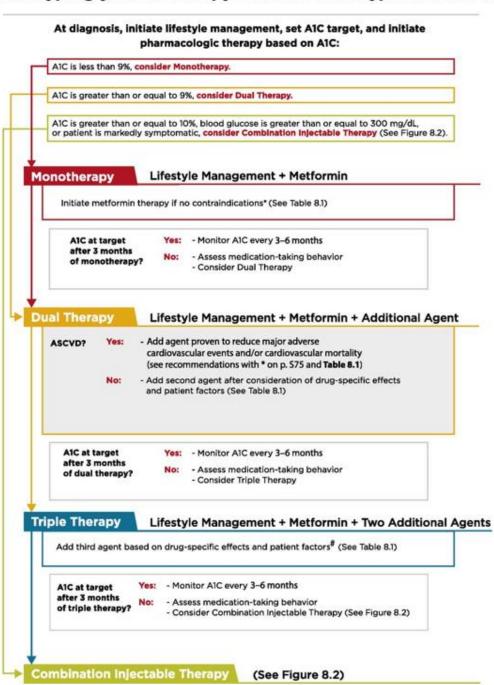
-) HFrEF (LVEF ≤ 40%)
- Acute coronary syn or MI, stable or unstable angina, CHD, other arterial revascularization, stroke, PAOD assumed to be atherosclerotic in origin
- 3) eGFR < 60 mL/min/1.73 m^2 , or uACR \geq 30 mg/g
- 1) Dapagliflozin, empagliflozin, ertugliflozin
-) Dapagliflozin, empagliflozin
-) Dulaglutide, liraglutide, semaglutide
- 7) Pioglitazone

¹⁾ Particularly heart failure with reduced ejection fraction (HFrEF, clinical diagnosis of HF and LVEF ≤ 40%).

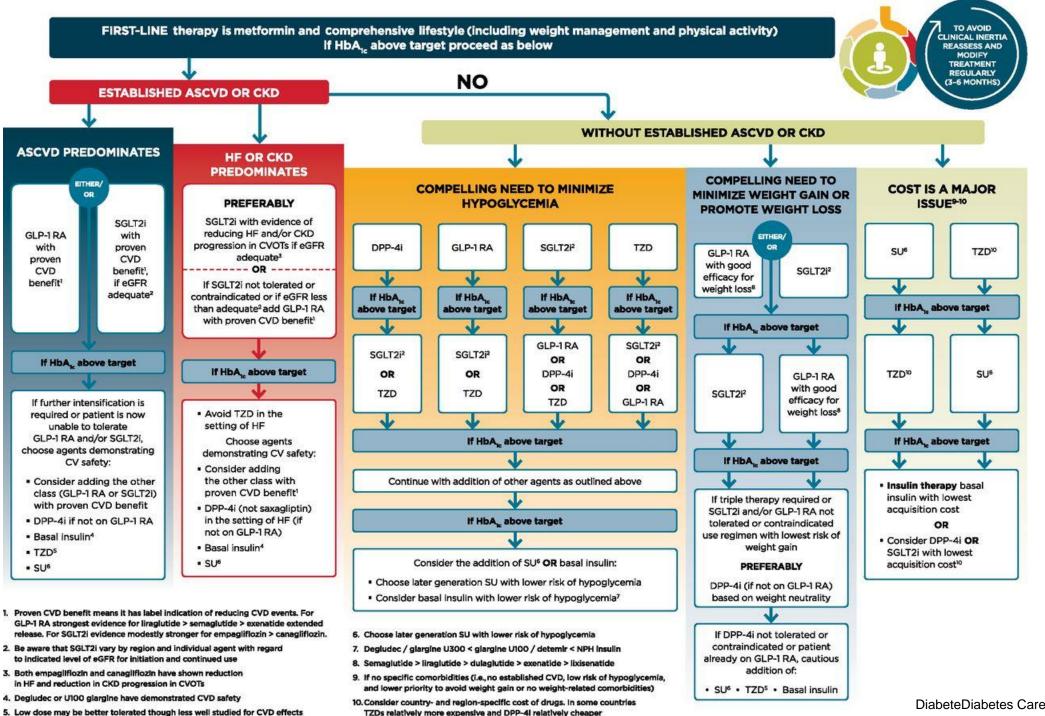
²⁾ A history of an acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

³⁾ eGFR < 60 mL/min/1.73 m² or urine albumin creatinine ratio ≥30 mg/g.

Antihyperglycemic Therapy in Adults with Type 2 Diabetes



2018년 ADA guideline



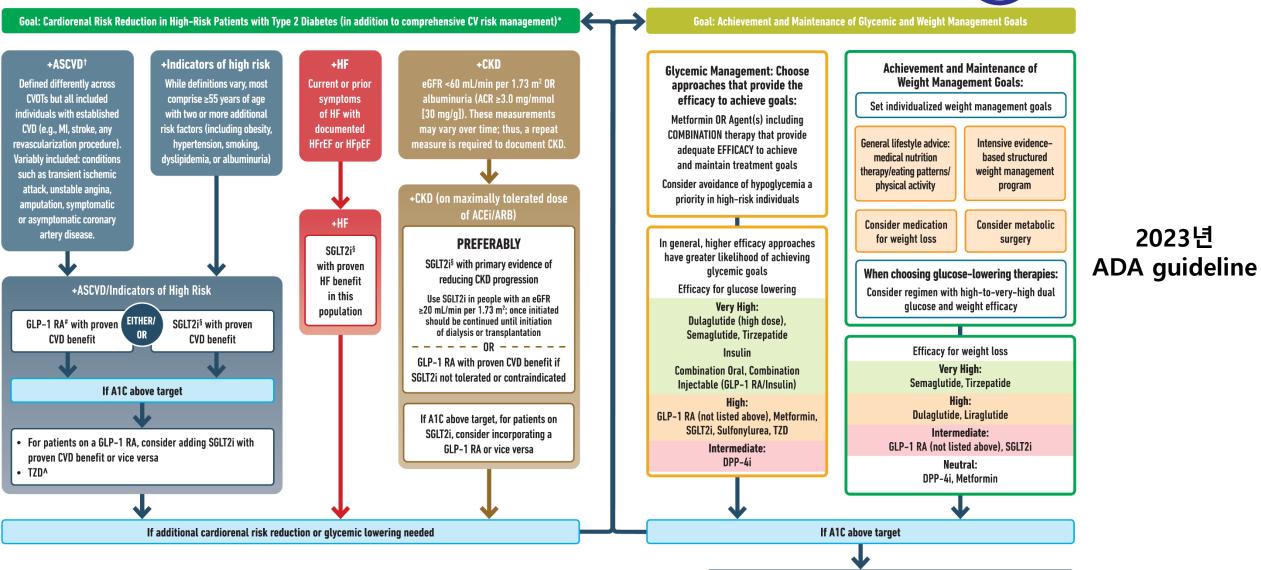
2019년 ADA guideline

DiabeteDiabetes Care. 2018;42(Supplement 1):S90-S102.

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)





* In people with HF. CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin: + A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; & For SGLT2i, CV/ renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Identify barriers to goals:

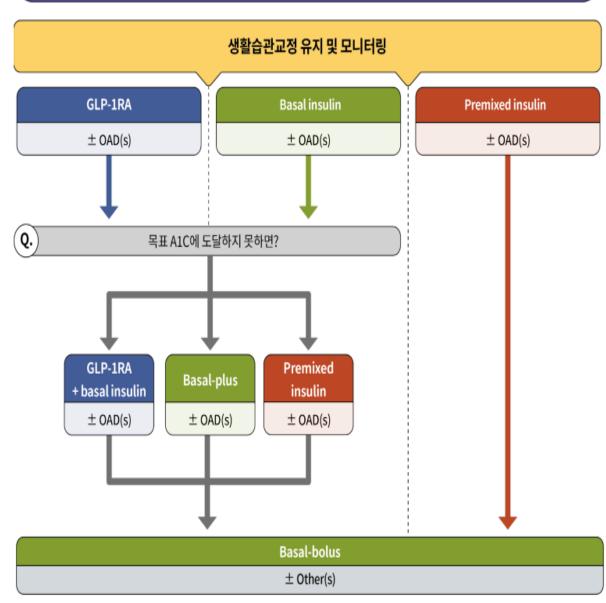
- Consider DSMES referral to support self-efficacy in achievement of goals
- . Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

Diabetes Care, 2022:46 (Supplement 1):S140-S157.

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		Fee:1	Hypogly-	W-:	CV effects		Renal effects		0 1/00	Cook	Clinical considerations			
		Efficacy ¹	cemia	Weight change ²	Effect on MACE	HF	Progression of DKD	Dosing/use considerations*	Oral/SQ	Cost	CUINCAL CONSIDERATIONS			
Metformi	n	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	Contraindicated with eGFR <30 mL/min per 1.73 m²	Oral	Low	 GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food Potential for vitamin B12 deficiency; monitor at regular intervals 			
SGLT2 inh	nibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	See labels for renal dose considerations of individual agents Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	 DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk Increased risk of genital mycotic infections Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable 			
GLP-1 RA	very high (intermediate to very high) (intermediate to very high) (iraglutide, semaglutide (SQ) (SQ) (SQ) (SQ) (SQ) (SQ) (SQ) (SQ)		 No dose adjustment for dulaglutide, 	SQ; oral (semaglutide)	Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) Counsel patients on potential for GI side effects and their typically temporary nature; prov guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mind eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges									
					Neutral: exenatide once weekly, lixisenatide		semaglutide (SQ)	impairment reporting severe adverse GI reactions			Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected			
GIP and G	ilp-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	See label for renal dose considerations No dose adjustment Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	 Risk of thyroid C-cell tumors in rodents; human relevance not determined Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected 			
DPP-4 inl	hibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment No dose adjustment required for linagliptin	Oral	High	 Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected Joint pain Bullous pemphigoid (postmarketing): discontinue if suspected 			
Thiazolid	inediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	No dose adjustment required Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	Congestive HF (pioglitazone, rosiglitazone) Fluid retention (edema; heart failure) Benefit in NASH Risk of bone fractures Weight gain: consider lower doses to mitigate weight gain and edema			
Sulfonylu (2nd gene		High	Yes	Gain	Neutral	Neutral	Neutral	Glyburide: generally not recommended in chronic kidney disease Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	 FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) Use with caution in persons at risk for hypoglycemia 			
Insulin	Human	High to	Yes	Gain	Neutral	Neutral	Neutral	Lower insulin doses required with a	SQ; inhaled	Low (SQ)	Injection site reactions Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs			
	Analogs	very high						decrease in eGFR; titrate per clinical response	SQ	High	myner nor o'nypogycenna wur numan mounn (arn or premizeu ionnuddons) vs. aliatugs			

Algorithm 3 | 주사제 포함한 치료



GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral anti-diabetic drug.

If injectable therapy is needed to reduce A1C1

Consider GLP-1 RA or GIP/GLP-1 RA in most individuals prior to insulin²

INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)

If above A1C target

Add basal insulin3

Choice of basal insulin should be based on person-specific considerations, including cost. Refer to **Table 9.4** for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.

Add basal analog or bedtime NPH insulin4

INITIATION: Start 10 units per day OR 0.1-0.2 units/kg per day

TITRATION:

- Set FPG target (see Section 6, "Glycemic Targets")
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

Assess adequacy of basal insulin dose

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime-morning and/or post-preprandial differential, hypoglycemia [aware or unaware], high variability)

- If above A1C target and not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes, either in free combination or fixed-ratio combination, with insulin.
- If A1C remains above target:

Add prandial insulin5

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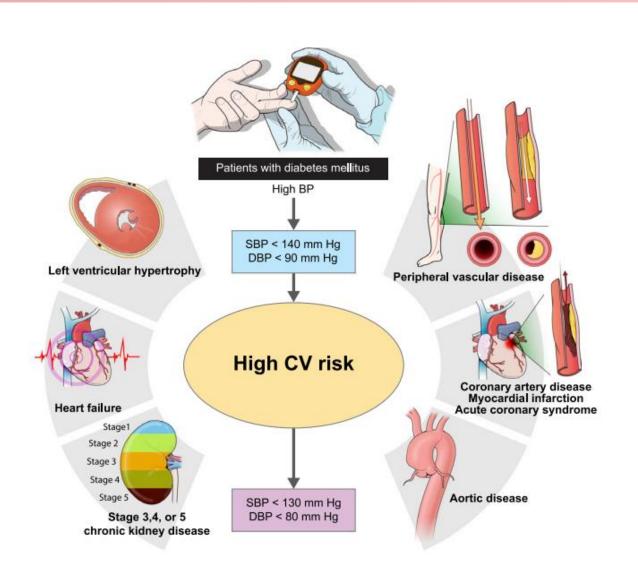
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Optimal target blood pressure (BP)

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (35)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE (36)	11,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single- pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	 Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (242)
HOT (37)	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	DBP target: ≤90 mmHg	 In the overall trial, there was no cardiovascular benefit with more intensive targets In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (43)	9,361 participants without diabetes	SBP target: <120 mmHg Achieved (mean): 121.4 mmHg	SBP target: <140 mmHg Achieved (mean): 136.2 mmHg	 Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) Intensive target reduced risk of death 27% Intensive therapy increased risks of electrolyte abnormalities and AKI
STEP (34)	8,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150 mmHg Achieved (mean): 135.3 mmHg	Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) Intensive target reduced risk of cardiovascular death 28% Intensive therapy increased risks of hypotension

ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; STEP, Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; T2D, type 2 diabetes.



Optimal target LDL-C

심혈관질환 위험도에 따른 LDL 콜레스테롤 및 non-HDL 콜레스테롤 목표치



위험도	LDL 콜레스테롤 (mg/dL) non-HDL 콜레스테롤 (LDL 콜레스테롤 농도(mg/dL) < 55 55-69 70-99 100-129 130-159 ≥ 160					
관상동맥질환1)*	< 55	< 85	생활습관 교정 및 투약고려	생활습관 교정 및 투약시작				
죽상경화성 허혈뇌졸중 및 일과성 뇌허혈발작* 경동맥질환* 말초동맥질환* 복부대동맥류* 당뇨병(유병기간 10년 이상 또는 주요 심혈관질환 위험인자 [†] 또는 표적장기손상을 동반한 경우) ²⁾	< 70	< 100	생활습관 교정	생활습관 교정 및 투약고려	생활습관 교정 및 투약시작	생활습관 교정 및 투약시작	생활습관 교정 및 투약시작	생활습관 교정 및 투약시작
당뇨병(유병기간 10년 미만, 주요 심혈관질환 위험인자 ⁺ 가 없는 경우)	< 100	< 130	생활 <u>습관</u> 교정	생활습관 교정	생활습관 교정 및 투약고려	생활습관 교정 및 투약시작	생활습관 교정 및 투약시작	생활습관 교정 및 투약시작
중등도 위험군(주요 심혈관질환 위험인자 [†] 2개 이상)	< 130	< 160						

< 190

저위험군(주요 심혈관질환 위험인자† 1개 이하)

< 160

^{*}LDL 콜레스테롤 기저치 대비 50% 이상 감소 시키는 것을 동시에 권고

[†]연령(남자 ≥ 45세, 여자 ≥ 55세), 조기 심혈관 질환 발생 가족력, 고혈압, 흡연, 낮은 HDL 콜레스테롤 수치 (< 40 mg/dL)

¹⁾ 급성심근경색증은 기저치 LDL 콜레스테롤 농도와 상관없이 스타틴을 투약

²⁾ 표적장기손상(알부민뇨, 만성콩팥병[추정사구체여과율 60 mL/min/1.73 m² 미만], 망막병증, 신경병증, 좌심실비대) 또는 3개 이상의 주요 심혈관질환 위험인자[†]를 동반한 당뇨병의 경우: LDL 콜레스테롤 목표치 < 55 mg/dL 선택적 고려 가능