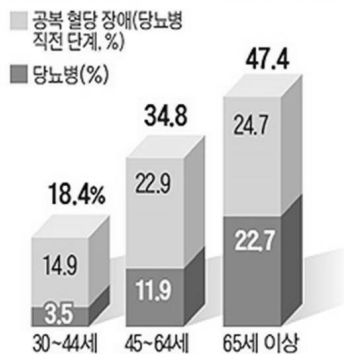


일차진료에서 당뇨병 환자의 최신 약물요법 가이드

이 덕 철

연세의대 가정의학교실

연령별 당뇨병 환자와 직전 단계 비율



FUTURE DIABETES POPULATION

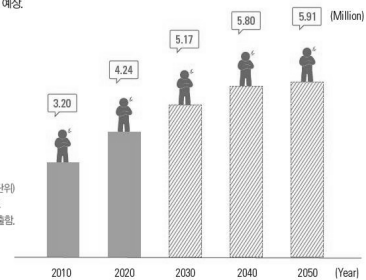
2050년 당뇨병 추정 인구

190%↑

- > 2050년도에는 당뇨병환자 수 약 600만명으로 추정
- > 2010년 기준 183% 증가한 수치이므로 향후 40년간 약 2배 증가 예상

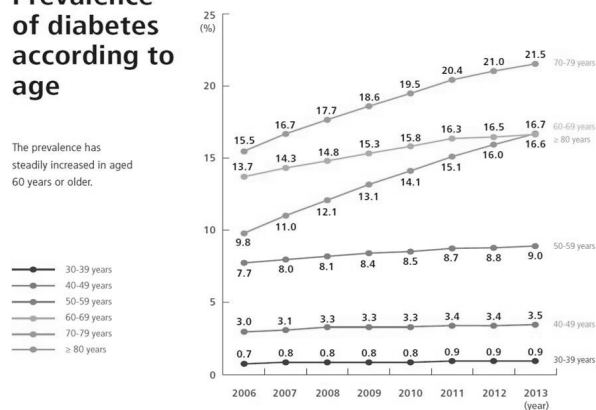
DIABETES FACT SHEET IN KOREA 2012

산출방식
2010년 생표, 연령별(10세 단위) 유행률을 기준으로 해당년도 인구수(추정치)에 곱하여 산출함.



Prevalence of diabetes according to age

The prevalence has steadily increased in aged 60 years or older.



KOREAN DIABETES FACT SHEET 2015

AWARENESS OF DIABETES

당뇨병 인지도

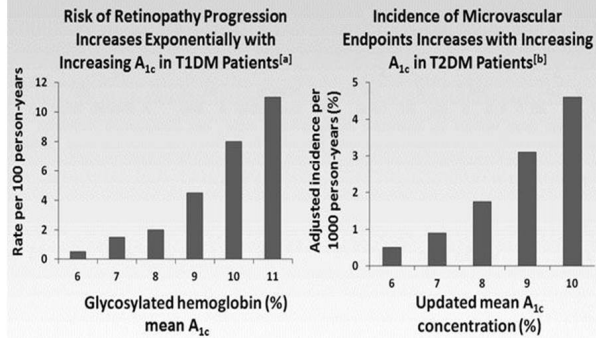
54.4% Age 30-44

- > 당뇨병환자 10명 중 3명은 본인이나 당뇨병이 있다는 사실을 모르고 있음. (당뇨병 인지도 73.4%)
- > 30~44세의 젊은 연령층에서 약 절반(45.6%)은 본인이 당뇨병임을 모르고 있음.

DIABETES FACT SHEET IN KOREA 2012



Persistently Elevated Glucose Levels Are Associated with Increased Risk for Complications



Impact of Intensive Therapy for T2DM Summary of Major Clinical Trials

Study	Microvasc	CVD	Mortality
UKPDS	↓ ↓	↔ ↓	↔ ↓
ACCORD	↓	↔	↑
ADVANCE	↓	↔	↔
VADT	↓	↔	↔

□ Initial Trial
■ Long Term Follow-up
* in T1DM

Principles of ADA & AACE Algorithms for Glycemic Control

- Minimize risk of **hypoglycemia**
- Minimize risk of **weight gain**
- Individualize and **personalize** management plan



Symptomatic and asymptomatic hypoglycemia



a plasma glucose concentration of ≤ 70 mg/dL

Severe hypoglycemia

- ◆ hypoglycemia requiring assistance from another person.
- ◆ cognitive impairment, loss of consciousness, seizure, coma, or death
- ◆ causes falls, motor vehicle accidents, or other injury.
- ◆ associated with greater risk of dementia

Diabetes Care 2016;39 (supple 1):539

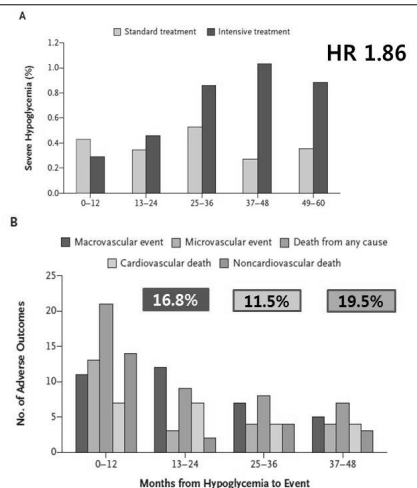
Major Hypoglycemia Significantly Increases the Risk for Adverse Outcomes in Patients with T2DM

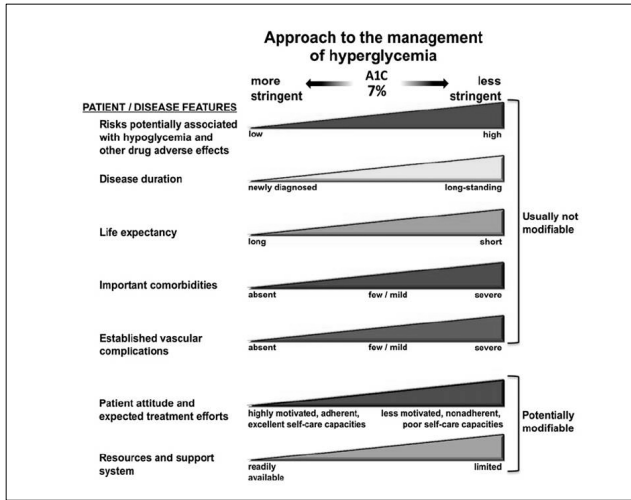
Hazard ratios for incident vascular outcomes and death among patients who had major hypoglycemia as compared with those who did not

Clinical outcome and interval after hypoglycemia	No. of events	Hazard ratio adjusted for treatment assignment (95% CI)	p-value
Macrovascular events	1147	4.05 (2.86 – 5.74)	< .001
Microvascular events	1131	2.39 (1.60 – 3.59)	< .001
Death from any cause	1031	4.86 (3.60 – 6.57)	< .001
Death from cardiovascular cause	542	4.87 (3.17 – 7.49)	< .001
Death from non-cardiovascular cause	489	4.82 (3.16 – 7.35)	< .001

N Engl J Med. 2010;363:1410-1418

Severe Hypoglycemia and Risks of Vascular Events and Death

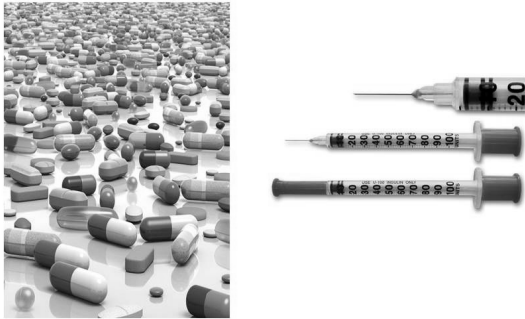




Glycemic targets in T2 DM

- **ADA 2016**
 - $HbA_{1c} < 7\%$ for most patients
 - HbA_{1c} 6.0-6.5% in patients with short duration, long LE, no CVD, single med.
 - HbA_{1c} 7.5-8.0% in patients with limited LE, severe hypoglycemia, high comorb. long standing DM, advanced vascular Cxs
 - FBS 80-130 mg/dL, postprandial 2hr < 180 mg/dL
- **AACE/ACE 2015**
 - $HbA_{1c} \leq 6.5\%$ for healthy patients
 - $HbA_{1c} > 6.5\%$ for concurrent illness at hypogly. Risk
 - FBS < 110 mg/dL, postprandial 2hr < 140 mg/dL

Diabetes medication Options



국내에서 사용 가능한 당뇨병약제, 9가지

- **Biguanides**
 - metformin
- **Sulfonylureas**
- **DPP-IV inhibitors**
 - Sitagliptin (januvia®)
 - Saxagliptin (onglyza®)
 - Linagliptin (trajenta®)
 - Vildagliptin (galvus®)
 - Alogliptin
- **GLP-1 receptor agonists**
 - Exenatide (Byetta®)
 - Liraglutide (victoza®)
- **Meglitinides**
- **Thiazolidinediones (TZDs)**
 - Only Pioglitazone
- **α -Glucosidase inhibitors**
 - Acarbose, Miglitol,
- **SGLT-2 inhibitors**
- **Insulin**
- **Bile acid sequestrants**
 - Colesevelam
- **Dopamine-2 agonists**
 - Bromocriptine

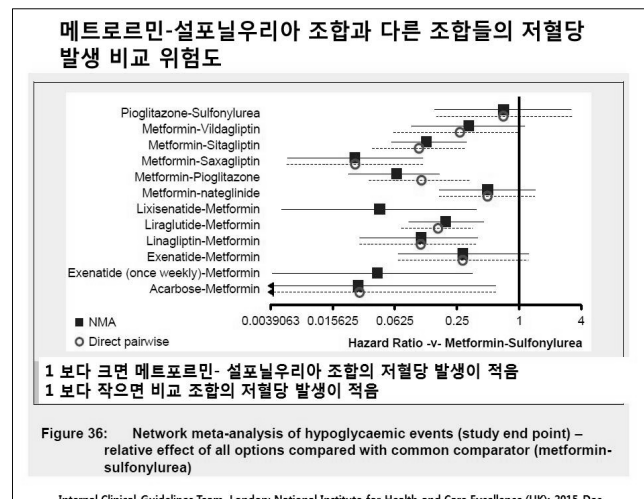
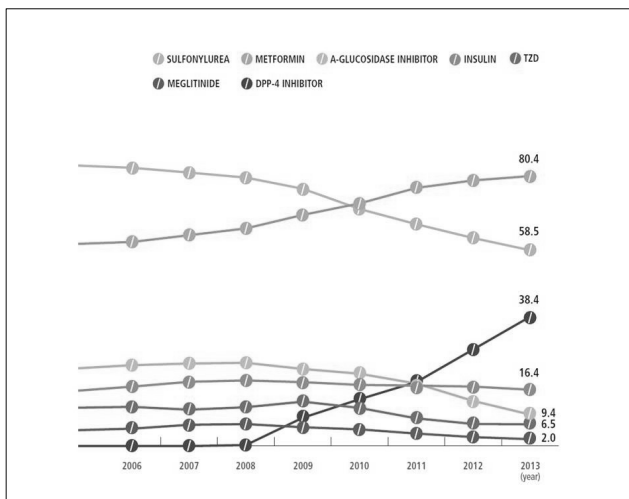
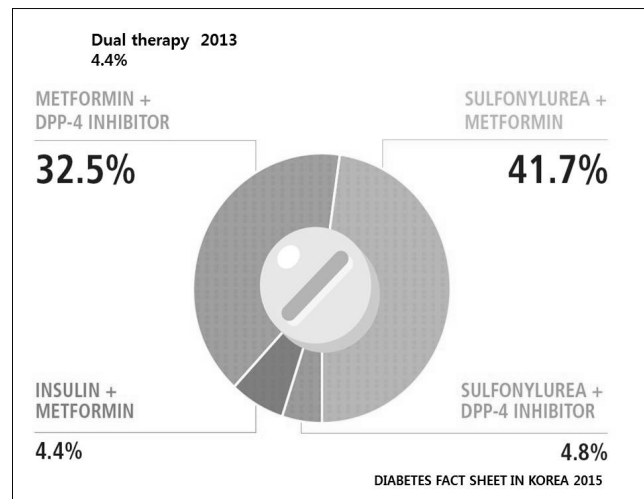
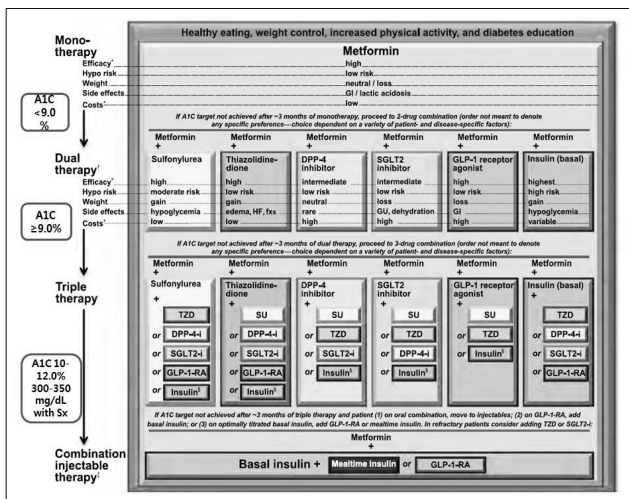
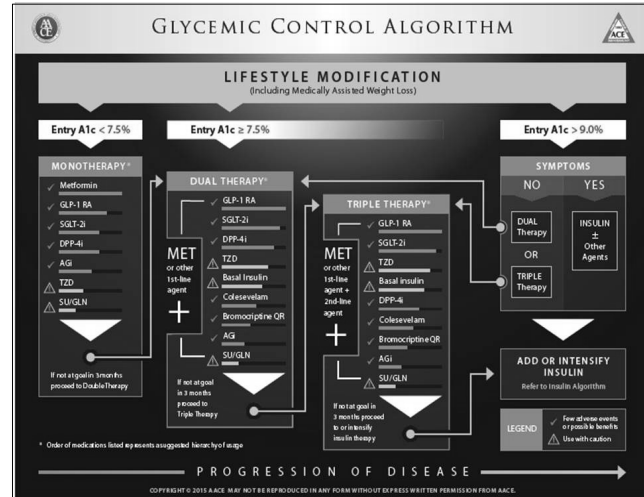
성분명 (상표명)	장점	단점
Biguanide		
Metformin (글루코팍자정®)	체중 불변, 저혈당 없음, 심혈관 합병증 및 사망률 감소, 내구성	위장관 부작용, 매우 드물게 젖산 산증, 비타민 B12 결핍, 신장기능 저하시 금기
Sulfonylurea (2세대)		
Glibenclamide (다오날정®)		
Glyburide (Micronase®)	일반적으로 잘 수용, 신속한 효과,	저혈당 위험 증가, 체중 증가, 혈당강화
Glipizide (Glucotrol®)	심혈관 합병증 및 사망률 감소	효과 내구성 저하
Gliclazide (다이마크통정®)		
Glimepiride (아마일정®)		
Meglitinides		
Repaglinide (프란단정®)	신속한 효과, 식후 혈당 강하	저혈당, 체중 증가, 자주 복용
Nateglinide (Starlix®)		
Thiazolidinediones (Glitazones)		
Pioglitazone (엑토스정®)	저혈당 없음, HDL-cholesterol 상승,	체중 증가, 부종, 심부전, 골결
Lobeglitazone (듀비에정®)	중성지방 저하	
α-Glucosidase inhibitor		
Acarbose (글루코박어정®)	심혈관 질환 위험 감소, 식후 혈당	소화장애 (장내가스, 설사), 자주 복용
Miglitol (글리톨정®)	저하, 저혈당 위험 감소, 체중 불변	
Voglibose (베이스정®)		

성분명 (상표명)	장점	단점
GLP-1 receptor agonist		
Exenatide (바이에타펜주®)	체중 감소, β 세포 수 및 기능 증가	소화관 부작용 (구역, 구토, 설사), 화장실 사려 보고, 주사제
Liraglutide (Victoza®)		
DPP-4 inhibitors		
Sitagliptin (자누비아®)		
Vildagliptin (가브스정®)	저혈당 없음, 체중 불변	간혹 두드러기, 혈관부종, 화장실 사려 보고
Saxagliptin (온글라이자정®)		
Linagliptin (트라젠타정®)		
Sodium glucose co-transporter type2 (SGLT2) inhibitors		
dapagliflozin (포시가정®)	체중감소, 저혈당 위험 감소,	생식기 감염증, 하부 요로감염
canagliflozin (Invokana™)	혈압감소	
empagliflozin (Jardiance®)		
lpragliflozin (Suglat®)		
Bile acid Sequestrants		
Colesevelam (Welchol™)	저혈당 없음, LDL-콜레스테롤 감소	변비, 중성지방 농도 상승, 다른 약제 흡수 방해
Dopamine-2 agonists		
Bromocriptine (팔로델정®)	저혈당 없음	어지러움, 설사, 구역, 피로감, 비염, 장기적 안전성 확립 안됨

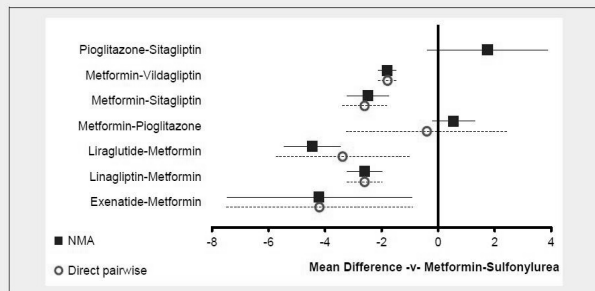
	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGI	TZD	SU	COLSVL	BCR-QR	INSULIN	PRAML
HYP	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/GU	Contra-indicated CVD Stage 3b, 4, 5	Exacerbate Contra-indicated CVD < 30	Ganital Myotic Infections	Dose Adjustment May be Necessary (Except Linagliptin)	Neutral	May Worsen Fluid Retention	More Hypo Risk	Neutral	Neutral	More Hypo Risk & Fluid Retention	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	?	Neutral	Safe	Neutral	Neutral
CVD	Benefit	Neutral	Increased LDL	Neutral	Neutral	Neutral	?	Neutral	Safe	Neutral	Neutral
BONE	Neutral	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Legend: Few adverse events or possible benefits (Grey), Use with caution (Light Grey), Likelihood of adverse effects (Dark Grey)

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메트로르민-설폰닐우리아 조합과 다른 조합들의 12 개월 후 체중 증가 비교

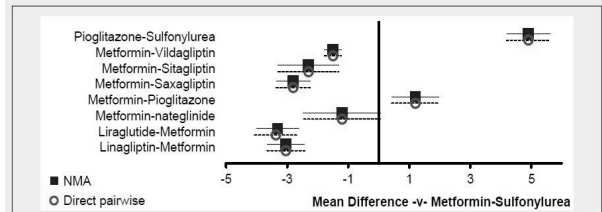


0 보다 크면 메트로르민-설폰닐우리아 조합의 체중 증가가 적음
0 보다 작으면 비교 조합의 체중 증가가 적음

Figure 44: Network meta-analysis of change in body weight (12 months) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

Internal Clinical Guidelines Team. London: National Institute for Health and Care Excellence (UK); 2015 Dec.

메트로르민-설폰닐우리아 조합과 다른 조합들의 24 개월 후 체중 증가 비교



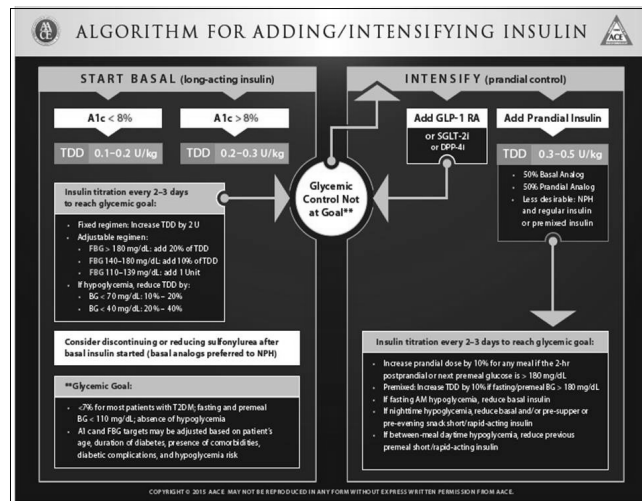
0 보다 크면 메트로르민-설폰닐우리아 조합의 체중 증가가 적음
0 보다 작으면 비교 조합의 체중 증가가 적음

Figure 46: Network meta-analysis of change in body weight (24 months) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

Internal Clinical Guidelines Team. London: National Institute for Health and Care Excellence (UK); 2015 Dec.

Insulin therapy

- Naïve DM with A1C $\geq 9.0\%$
- Significant hyperglycemia with A1C $\geq 10.0-12.0\%$
- Inability to achieve target A1C (esp. A1C $\geq 8.5\%$) despite the use of ≥ 2 OADs or GLP-1 therapy.
- Consider patient motivation, CVD history, hypoglycemia risk, age, and general well-being
- Add on therapy with basal insulin at night



Major adverse effects of Insulin

- **Hypoglycemia**
7-15% of T2DM patients experience ≥ 1 /year
1-2% of them have severe hypoglycemia associated with intensive target, SU use, CR, renal dysfunction, exercise, alcohol, diabetes duration, cognitive impairment
increase mortality rate 2-4 folds
- **Weight gain**
1-3 kg more weight
- **Progressive worsening of retinopathy (5%)**
- proliferative retinopathy and A1C $> 10\%$

Special considerations

- **old Age**
- individualized by comorbidities, polypharmacy, limited LE, hypoglycemia
- Target HbA_{1c} 7.5-8.0% (American Geriatric Society)
- 8.5-9.0% is acceptable in debilitated elderly.
- **Weight**
- overweight or obesity (~80%) in T2 DM
- GLP-1 receptor agonist, DPP-4i, SGLT2i, AGI
- avoid SU, glinide, TZD, insulin

• **Coronary artery disease**

- Avoid SU, glinide, insulin (hypoglycemia, K channel)
- CV benefit
 - metformin, pioglitazone unless heart failure, bromocriptine (reduce CV events by 40%)
- CV risk benefit
 - GLP-1 RA and DPP-4i, but no long term data
 - colsevelam reduce LDL-C

• **Heart failure**

- Avoid TZDs
- metformin can be used unless ventricular dysfunction

• **Chronic kidney disease**

- extreme caution with use of SU, glinide and insulin (hypoglycemia)
- avoid metformin
 - if $cr \geq 1.5 \text{ mg/dL}$ in men, $cr \geq 1.4 \text{ mg/dL}$ in women
 - if $GFR < 30 \text{ ml/min}$
- reduce dose if $GFR < 45 \text{ ml/min}$ (NICE guideline)
- avoid exenatide if $GFR < 30 \text{ ml/min}$ (stage IV-V)
- Linagliptin, liraglutide, pioglitazone may be used
- reduced dose DPP-4i except Linagliptin if $GFR < 50 \text{ ml/min}$, and stop if $GFR < 50 \text{ ml/min}$,

• **Liver disease**

- insulin preferred in advanced liver disease
- pioglitazone for NAFLD with mild liver dysfunction but avoid $ALT > 2.5$ times of NL,
- avoid SU in severe hepatic dysfunction (risk of hypoglycemia)
- avoid vildagliptin in hepatic impairment
- other DPP-4is and GLP-1 RA can be used with no dose adjustment unless history of pancreatitis

• **Hypoglycemia risk**

- 3 fold risk in intensive management
- increased risk of brain dysfunction
- more dangerous in elderly
- may lead to dysrhythmia, dizziness, confusion, accidents and falls
- increased infection (aspiration pneumonia)
- work disability, erosion of confidence

• **hypoglycemia and weight gain**

- SU for possible increased risk of MI, CHF, mortality (HR 1.30-1.68)
- insulin for possible increased risk of CV
- avoid SU metiglinide if possible
 - favor AACE algorithm than ADA statement
- insulin use: fail in 3 oral drug combination, acute infection,
- favor DPP-4i, SGLT-2i GLP-1 RA, metformin