Educational approaches to the use of non-insulin anti-diabetes drugs

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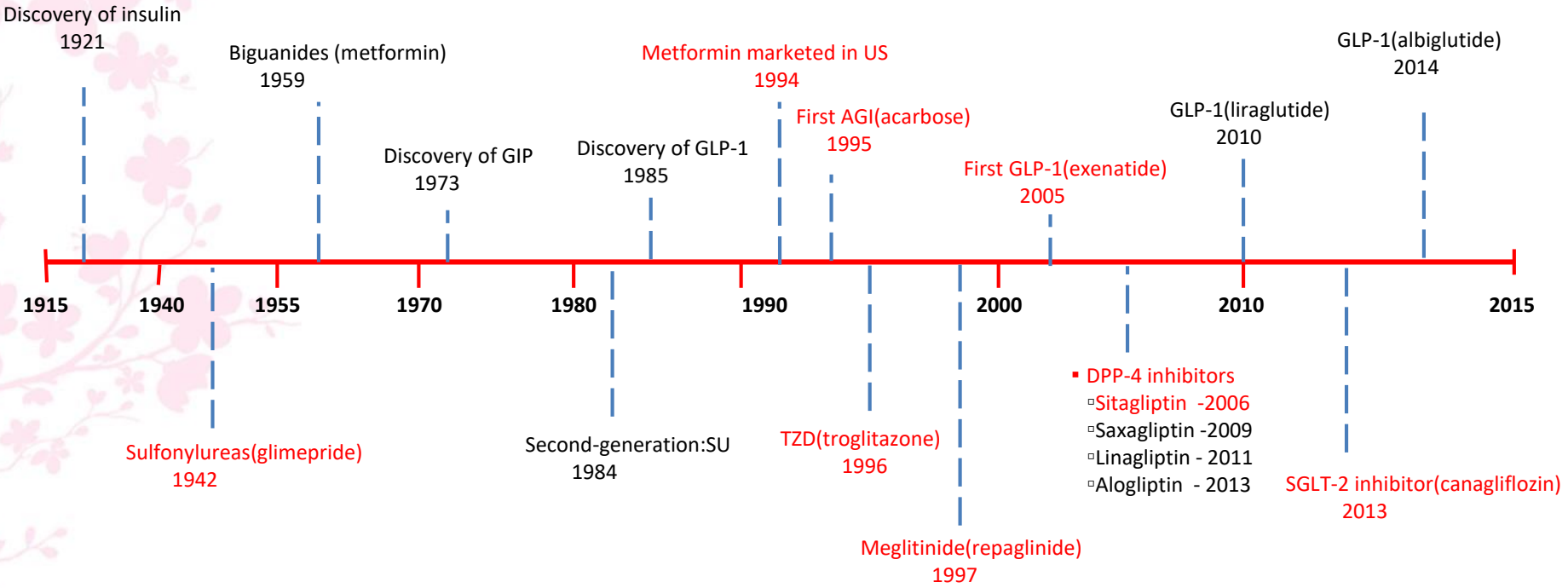
Contents

- History of diabetes medication
- Principles of drug treatment
- Considerations for drug selection
- Characteristics of Medicines
- Pharmacology Management

History of diabetes medications



John R. White, Jr. Diabetes Spectr 2014;27:82-86

약물 치료의 원칙

- 당뇨병성 합병증을 예방하기 위해 철저하게 혈당을 조절해야 한다. (A)
- 혈당 조절 목표 : HbA1c 6.5%이하이다. (A)
- 당뇨병 진단 초기부터 적극적인 생활습관 개선 및 적절한 약물치료가 필요하다. (A)
- 경구약제 단독요법 시 초치료로 메트폴민을 우선적으로 고려하나, 환자 상태에 따라 적절한 약제를 선택한다. (A)
- 약제의 작용기전과 효능,부작용,비용 및 환자의 특성과 선호도를 고려하여 적절한 단독 또는 병합요법 약제를 선택한다. (E)

대한당뇨병학회, 당뇨병진료지침.2015

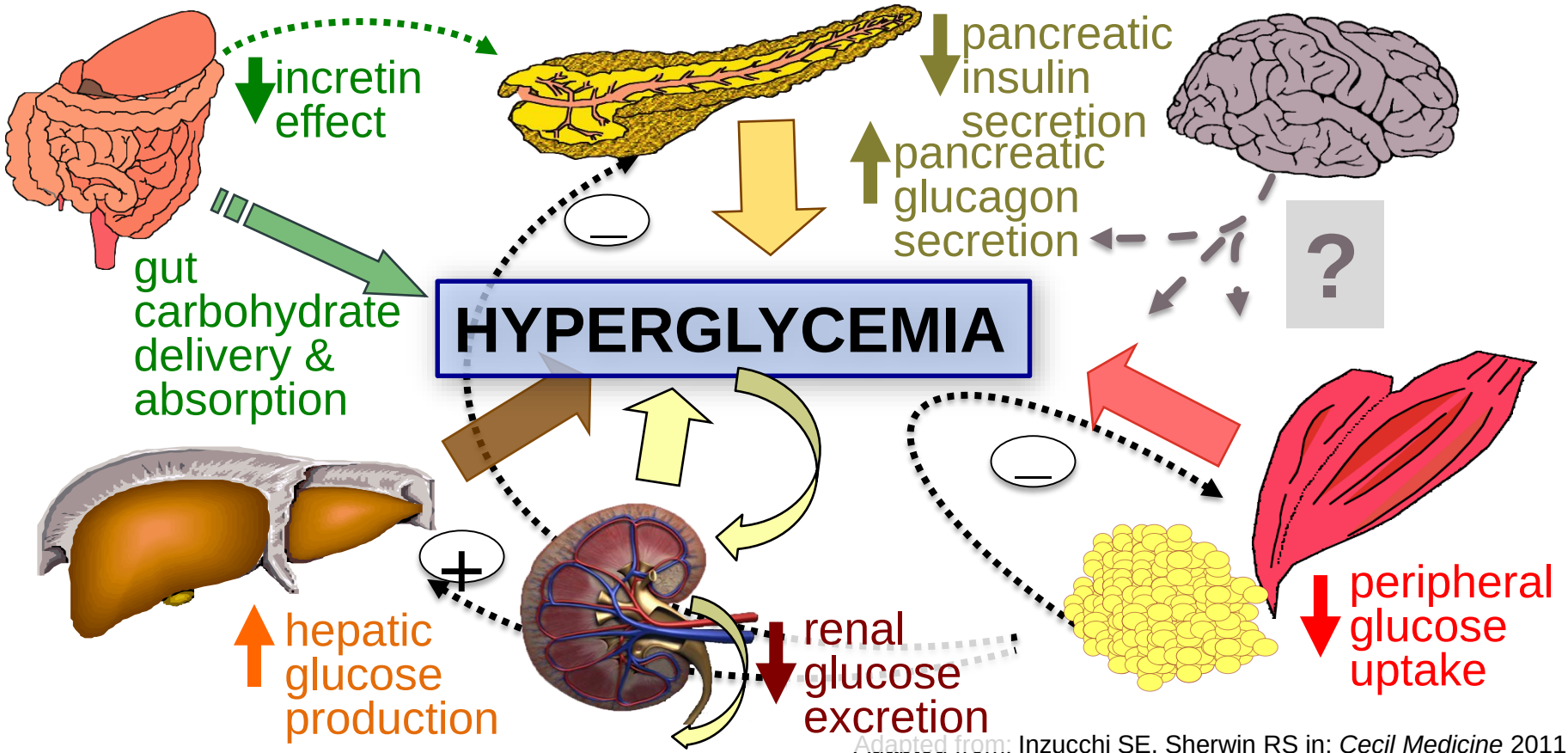
약제선택 시 고려사항

환자의 연령 (남은 삶의 여명, 저혈당 위험성)
당화혈색소 정도, 공복 및 식후 고혈당 정도
비만 및 대사증후군 여부
인슐린 분비능
간기능 및 신장기능 이상 여부
경제적 측면

부작용 없이 혈당조절

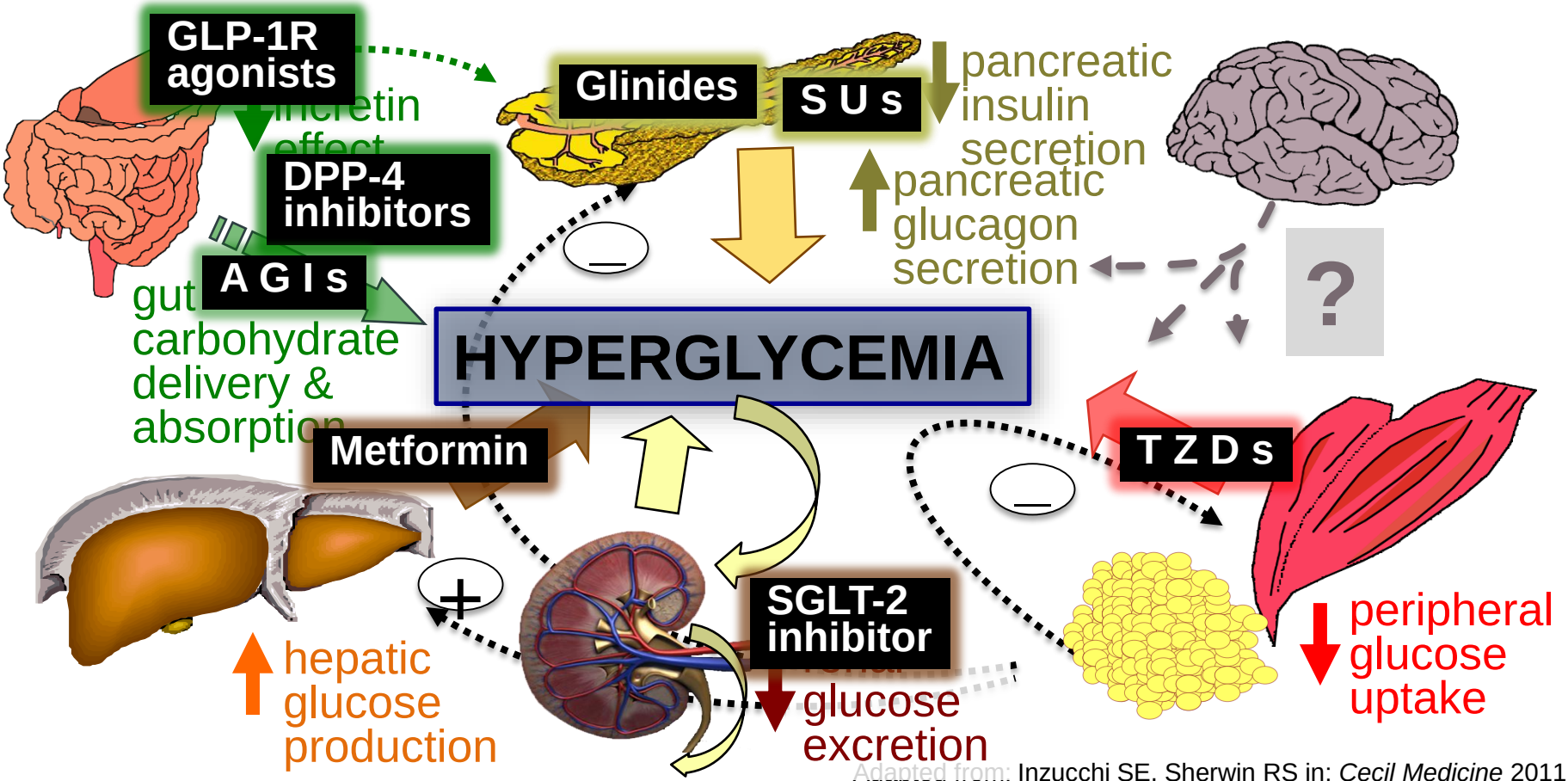
대한당뇨병학회, 당뇨병진료지침.2015

Hyperglycemia in T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Anti-hyperglycemic drug



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Non-insulin anti-diabetes drugs characteristics

Biguanides
Sulfonylureas
Meglitinide derivatives
Alpha-glucosidase inhibitors
Thiazolidinediones (TZDs)
Dipeptidyl peptidase IV (DPP-4) Inhibitors
Glucagonlike peptide–1 (GLP-1) agonists
Selective sodium-glucose transporter-2 (SGLT-2) inhibitors

Biguanides(metformin)

▪ Mechanism of action

- ↓hepatic glucose production

▪ Efficacy

-↓ HbA1c 1~2% (lowers fasting glucose)
-rare hypoglycemia
-Weight natural or loss (2~3kg)
-↓ CVD event(UKPDS)

▪ Advers effect

-GI side effect : N/V, diarrhea, abdominal pain
-**Vitamin V12 deficiency : anemia, peripheral neuropathy**
-Lactic acidosis(rare)

▪ Contraindicated

- eGFR<30ml/min (Cr ≥1.4mg/dl women, ≥1.5mg/dl men)
-Discontinue with IV contrast studies
: Hold day of procedure, restart 48hours later

▪ Cost : **Low**

Standards of Medical care in diabetes,2017
Oral and Injectable (Non-insulin) Pharmacological Agents for Type 2 Diabetes,2016

- Biguanides
- **Sulfonylureas**
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)
- Dipeptidyl peptidase IV (DPP-4) Inhibitors
- Glucagonlike peptide–1 (GLP-1) agonists
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Sulfonylureas

- **Mechanism of action**

- ↑ Insulin secretion

- **2nd generation : Glyburide(Diabeta), Glipizid(Glucotrol), Glimepiride(Amaryl)**

- **Efficacy**

-↓ HbA1c 1~2% (lowers fasting and postprandial glucose)

-↓ Microvascular risk(UKPDS)

- **Advers effect**

-Common: hypoglycemia, weight gain

-Less common : rash,headache, N/V, photosensitivity

- **Contraindicated**

- Patient with hypoglycemia unawareness(e.g.eldery)
- Poor renal function

- **Cost : Low**

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Meglitinides

▪ Mechanism of action

- ↑ Insulin secretion :약효가 빠르고 작용시간이 짧다.

▪ Repaglinide(Novonom) and Nateglinide(Fastic)

▪ Efficacy

-↓ HbA1c repaglinide 1% , nateglinide 0.5%

-↓ postprandial glucose (short acting: peak30~60min,short half-life 60~90min)

-Dosing flexibility

▪ Advers effect

-Hypoglycemia and weight gain(less than SUs)

-Increase serum uric acid

-Frequent dosing schedule

▪ Contraindicated

: Patient with hypoglycemia unwareness

: Poor renal function(nateglinide), moderate to severe liver disease

▪ Cost : **Moderate**

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Alpha-glucosidase inhibitors

- **Mechanism of action**

- Slows intestinal carbohydrate digestion/absorption

- **Acarbose, Boglibos(Basen), Miglitol(Glyset)**

- **Efficacy**

-↓ HbA1c 0.5~1% , rare hypoglycemia

-↓ Postprandial glucose

- **Advers effect**

-Common: gas, bloating, abdominal pain

-Freguent dosing schedule

- **Precautions**

- Short-bowel syndrom, increase liver transaminases(acabose)

- **Cost : Low to moderate**

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Thiazolidinediones (TZDs)

- **Mechanism of action**

- ↑ Insulin sensitivity of muscle, fat, and liver tissues

- **Pioglitazone (Actos),Rosiglitazone(Avandia), Lobeglitazone(Dubia)**
  : Increased risk of MI (rosiglitazone)
- **Efficacy**

-↓ HbA1c 1~1.5%, rare hypoglycemia
-Durable effect (low fasting and postprandial glucose)
-↓Triglycerides, potential decrease in MI (pioglitazone)

- **Advers effect**

-Weight gain (2~3kg)
-Edema/heart failure/Bone fractures
-↑LDL-C (rosiglitazone) ,bladder ca (pioglitazone)

- **Cost : LOW**

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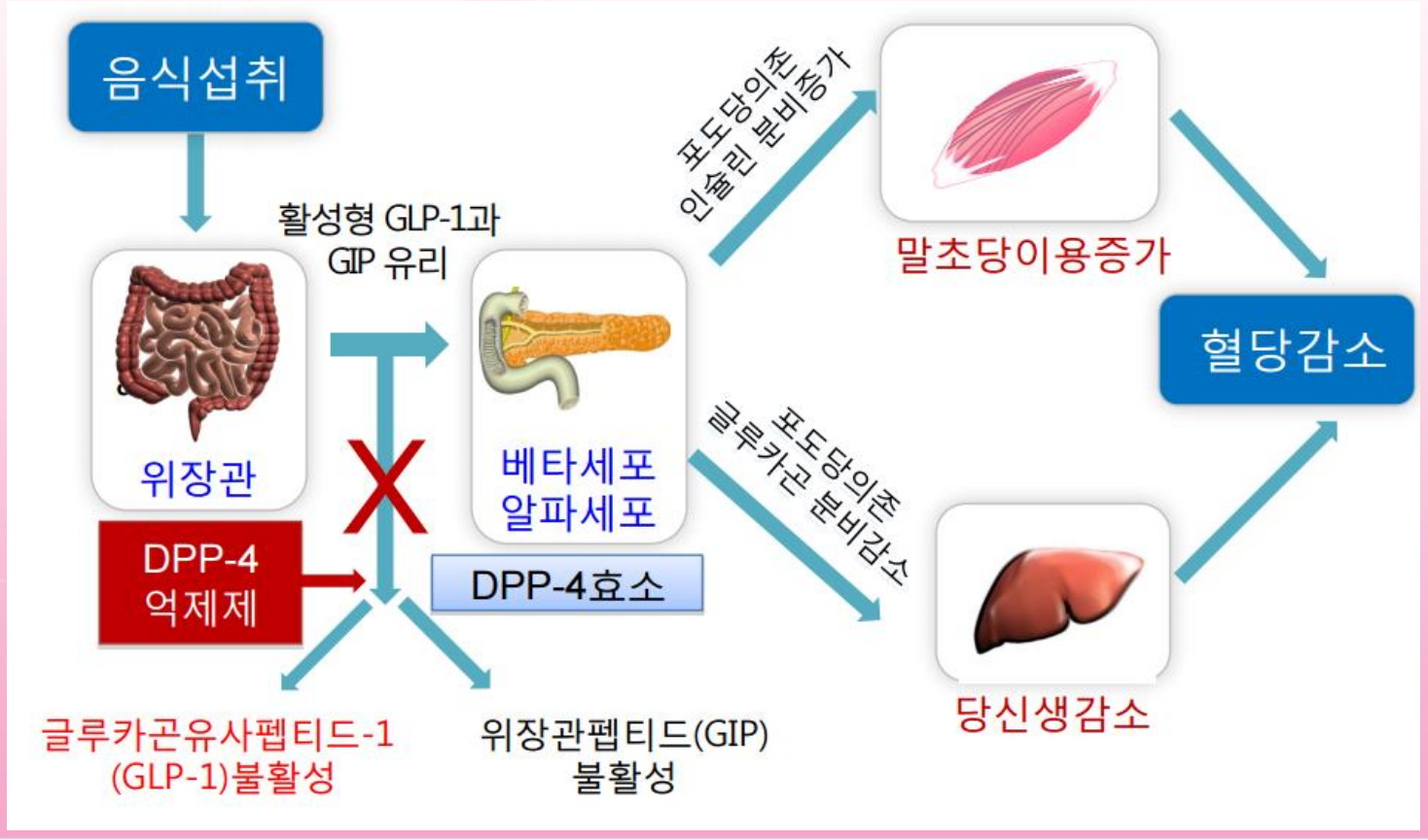
DPP-4 Inhibitors: Physiologic Action



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DPP-4 Inhibitors

Mechanism of action

- ↑ Insulin secretion,↓glucagon secretion
- **Sitagliptin(Januvia), Saxagliptin(Onglyza), Liragliptin(Trazenta), Alogiptin(Nesina) Vildagliptin(Galvus), Zemigliptin(Zemiglo)**

Efficacy

-↓ HbA1c 0.5~0.8% (lowers postprandial glucose)

-rare hypoglycemia, Well tolerated

Advers effect

-Angioedema/urticaria/immune-mediated dermatological effect

-? Acute pancreatitis

- ↑ Heart failure hospitalization (saxagliptin, ? Alogliptin)

Cost : **High**

Standards of Medical care in diabetes,2017

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Efficacy of DPP4 inhibitors as add-on to Metformin

Drug	No. of patients	Study duration	Baseline HbA1c level	Study group	Control	Reduction of HbA1c	Reference no.
Sitagliptin	701	24 wk	8.0%	MET + Sita 100 mg	MET + Placebo	-0.65%	[28]
	273	18 wk	7.7%	MET + Sita 100 mg	MET + Placebo	-0.51%	[29]
Vildagliptin	544	24 wk	8.4%	MET + Vilda 50 mg	MET + Placebo	-0.7%	[30]
				MET + Vilda 100 mg		-1.1%	
	370	24 wk	8.5%	MET + Vilda 100 mg	MET + Placebo	-0.83%	[31]
Saxagliptin	743	24 wk	8.0%	MET + Saxa 2.5 mg	MET + Placebo	-0.73%	[32]
				MET + Saxa 5 mg		-0.83%	
				MET + Saxa 10 mg		-0.72%	
Linagliptin	701	24 wk	8.1%	MET + Lina 5 mg	MET + Placebo	-0.64%	[33]
Alogliptin	527	26 wk	7.9%	MET + Alo 12.5 mg	MET + Placebo	-0.5%	[34]
				MET + Alo 25 mg		-0.5%	

John Gerich, Diabetes Research and Clinical Practice 90 (2010) 131–140

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Comparison between DPP4I

	Januvia	Galvus	Onglyza	Trajenta	Zemiglo	Nesina
성분명	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin	Zemigliptin	Alogliptin
국내 허가	2008	2008	2011	2012	2012.12	2014
배설 경로	신장	신장	신장	담즙과 위장관	간과 신장	신장
반감기 (hr)	8-14hrs	2-3hrs	2.5(3.1)hrs	120hrs	17-21hrs	12.5~21.1hrs
판매	MSD 대웅제약	노바티스 한독	BMS 아스트라	베링거인겔하임 릴리/유한양행	LG	다케다
가격 (1일)	100mg/924원	453 x 2 =906원	5mg / 850원 2.5mg/588원	5mg / 831원	50mg / 815원	25mg/759원
이상 반응	두통 감염 췌장염 저혈당	간기능 이상 췌장염 알러지 어지러움	상부호흡기감염 비뇨기 감염 두통 저혈당	저혈당	신장애 심부전 급성췌장염	간기능이상 상기도감염 췌장염
임부	권장안됨	사용안됨	B등급	B등급	사용안됨	B등급

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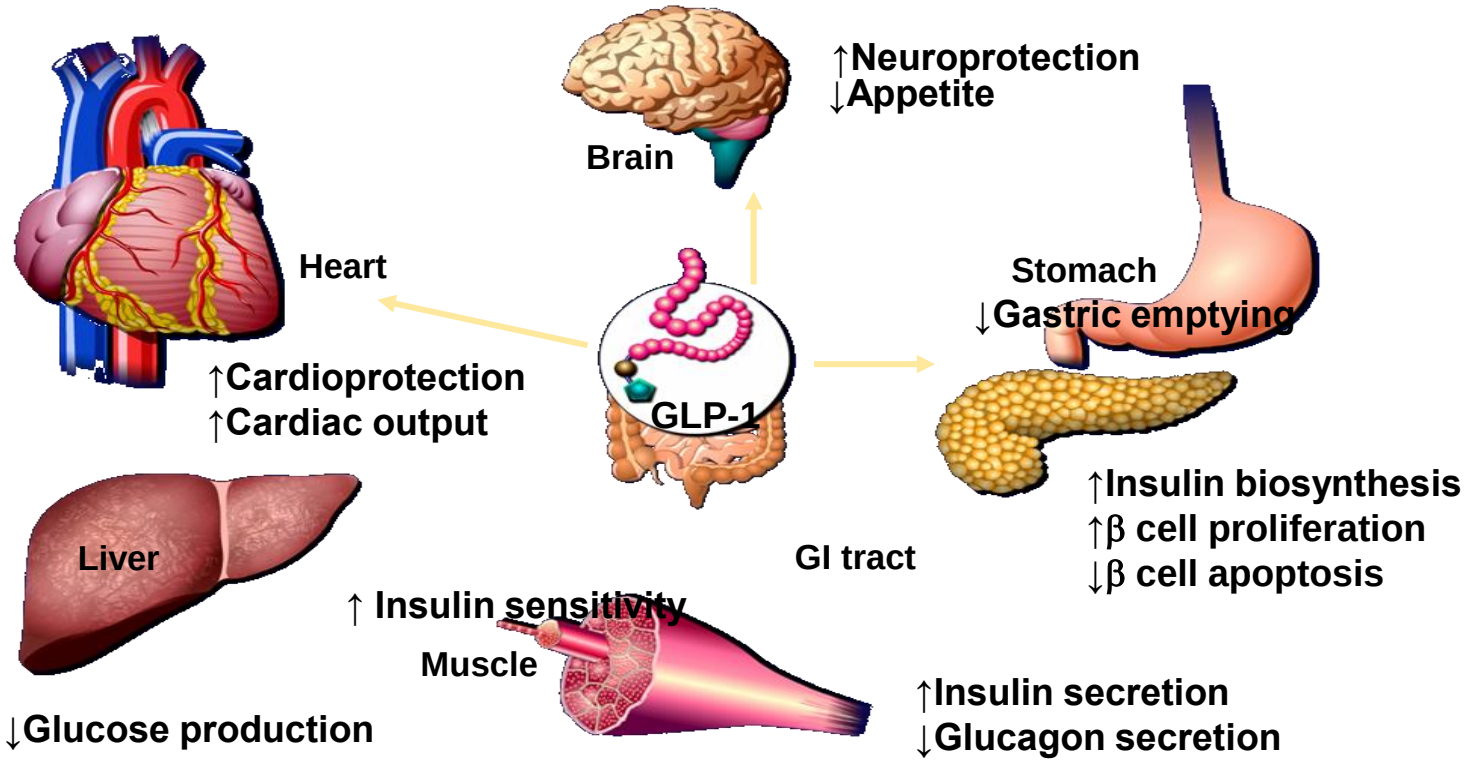
- Selective sodium-glucose transporter-2 (SGLT-2) inhibitors

GLP-1 agonists



Drucker DJ. Cell Metab. 2006;3:153-165.

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GLP-1 agonists

Mechanism of action

- ↑ Insulin secretion,↓glucagon secretion, slows gastric emptying, ↑satiety

Exenatide,Liraglutide,Albiglutide,Lixisenatide,Dulaglutide

Efficacy

-↓ HbA1c 1~1.5%, Rare hypoglycemia
-↓ Weight (1~3kg)
-↓ Postprandial glucose
-↓ Some cardiovascular risk factor, lower CVD event and mortality(Liraglutide, LEADER)

Advers effect

- GI side effect : N/V, diarrhea
- ↑Heart rate
-?Acute pancreatitis
-C-cell hyperplasia/medullary thyroid tumors in animals
-Injectable, Training reguirements

Cost : **High**

Standards of Medical care in diabetes,2017

Short-Acting GLP-1 vs. Long-Acting GLP-1

Short-acting GLP-1 RAs
(exenatide BID, lixisenatide*)

Long-acting GLP-1 RAs
(liraglutide, exenatide QW, albiglutide, dulaglutide)

Similarities

Differences

- Biguanides
- Sulfonylureas
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)
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- **Glucagonlike peptide–1 (GLP-1) agonists**
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GLP-1 RA Pharmacokinetic Profile

	Dosing	Half-life	Tmax	Renal dosing	Side effect	Cost
Short - acting (4-6hrs) : postprandial glucose ↓HbA1c 0.8~1.5%						
Exenatide (Byetta)	5 μg BID 10 μg BID	2.4Hours	2.1hours	Not recommend If CrCl <30ml/min	Weight loss GI upset	90720원
Lixisenatide (Lyxumia)	10 μg QD 20 μg QD	3hours	1.0-3.5hours	Not recommend If CrCl <30ml/min	Weight loss nausea	39501원
Intermediate - acting (24hrs) : fasting and postprandial glucose ↓ HbA1c 0.8~1.8%						
Liraglutide (Victoza)	0.6 mg QD 1.2mg/ 1.8 mg QD	13 hours	8-12 hours	No dose adjustment Caution :renal impairment	Weight loss nausea	80000원
Long – acting (7day)						
Dulaglutide (Trulicity)	0.75 mg QW 1.5 mg QW	5 days	3-5 days	No dose adjustment	Weight loss nausea	23560원
Albiglutide (Eperzan)	30 mg QW 50 mg QW	~ 5 days	3-5 days	Not recommend If eGFR <15ml/min	Weight loss nausea	21168원
Exenatide (Bydureon)	2 mg QW	7-14 days	6-7 weeks	Not recommend If CrCl <30ml/min	Weight loss nausea	

BID=twice daily, OD=once daily, OW=once weekly, Tmax=time to reach maximum concentration

Phamacologic treatment of type2diabetes:injectable medications.phamacother 2015;49:700-714

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Injection Site Reactions

Adverse reactions	Albiglutide [30]		Dulaglutide [35]			Liraglutide [22]	Exenatide QW [26]	Exenatide BID [17]	
N	Albiglutide N=923, %	Placebo N=468, %	Dulaglutide 0.75 mg N=834, %	Dulaglutide 1.5 mg N=836, %	Placebo N=568, %	Liraglutide N=497, %	Exenatide N=248, %	Exenatide N=963, %	Placebo N=483, %
Diarrhea	13.1	10.5	8.9	12.6	6.7	17.1	10.9	13	6
Nausea	11.1	9.6	12.4	21.1	5.3	28.4	11.3	44	18
Vomiting	4.2	2.6	6.0	12.7	2.3	10.9	NA	13	4
Injection-site reaction or nodules	10.5	2.1	0.5	0.5	0	NA	10.5	NA	NA

Drugs in Context. 2015;4:212283

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coming GLP-1 RAs + Insulin Mixture

Insulin degludec + liraglutide = Xultophy*

Insulin glargine + lixisenatide = Lixilan*

* Xultophy and Lixilan are not approved in Korea.

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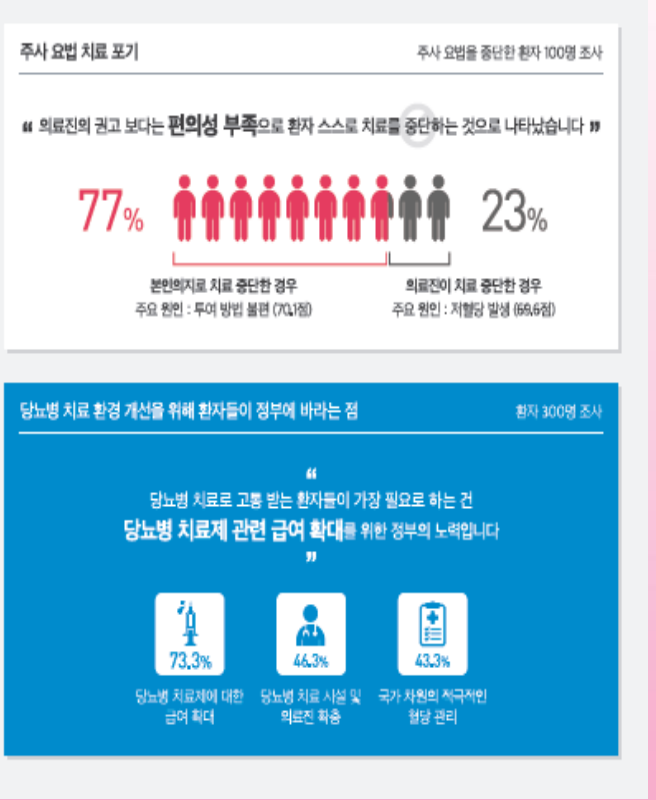
주사제의 한계성



한국당뇨환우연합회, 제2형 당뇨병 환자 설문조사 인포그래픽, 2015.06

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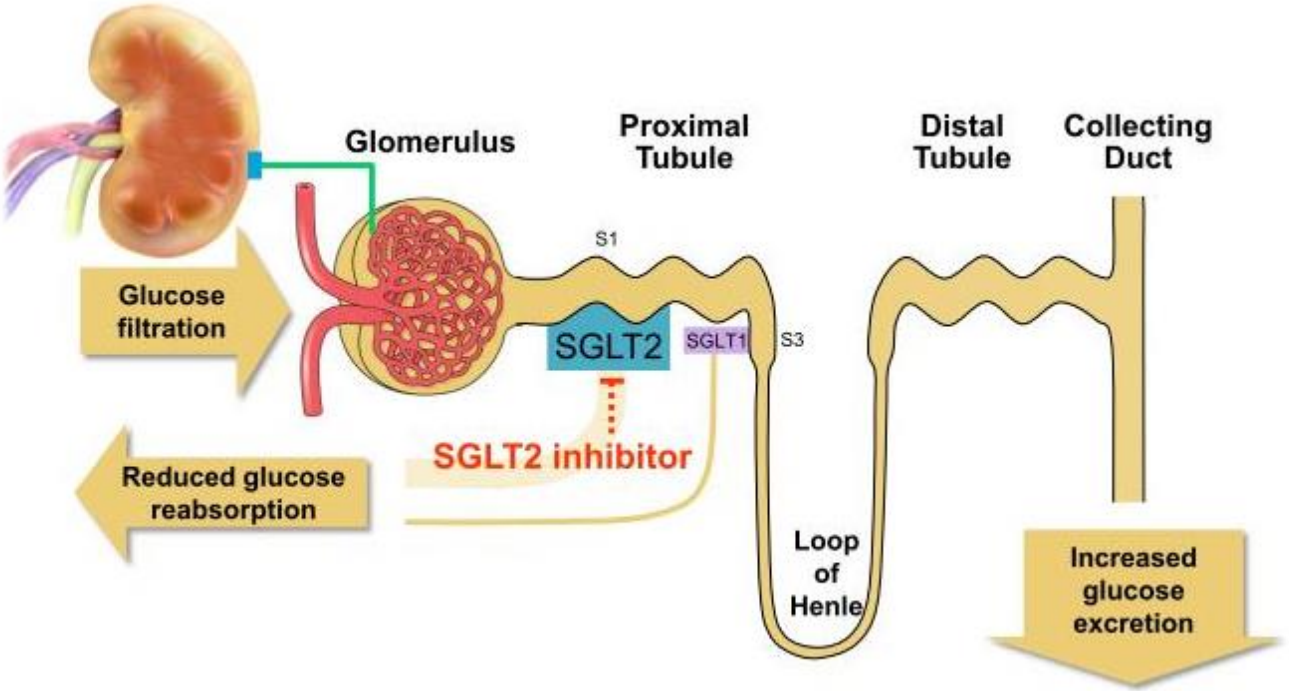
SGLT-2 inhibitors: Physiologic Action



1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21; 4. S Nair, Practical Diabetes Int 2010; 27(7): 311–316

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SGLT-2 inhibitors

Mechanism of action

- Blocks glucose reabsorption by the kidney, increasing glucouria

Canagliflozin(Invocana), Dapagliflozin(Forxiga), Empagliflozin(Jardiance)

Efficacy

-↓ HbA1c 0.5~1%, rare hypoglycemia (lowers fasting glucose)
-↓ Weight (3~4kg), ↓ Blood pressure(3~6mmHg SBP)
-↓ CVD event and mortality(empagliflozin, EMPA-REG outcom)

Advers effect

-Genitourinary infection, Polyuria
-Volume depletion/hypotension/dizziness
-↑LDL-C , ↑Creatinine
-DKA, urinary tract infections leading to urosepsis, pyelonephritis

Contraindicated

-Renal impairment : GFR<60ml/min avoid dapagliflozin
-GFR <45ml/min avoid canagliflozin and empagliflozin
-Bladder cancer (dapagliflozin), stroke(canagliflozin)

Cost : **High**

Pharmacologic Approaches to Glycemic Treatment

Pharmacologic Therapy for type1 diabetes

- Metformin
  - Uncontrolled DM, overweight/obese patients
    -Reduce insulin requirement (6.6unit/day, $p<0.001$) , weight and total and LDL-C
    -Not to improved glycemic control (HbA1c reduction:0.11%, $p=0.42$)
    -Not FDA approved
- Increatin-Based Therapy
  - GLP-1 receptor and DPP-4 inhibitors :Being studied, Not FDA approved
    -protection of β-cell mass and suppression of glucagon release
- Sodium-Glucose Contansporter 2 inhibitors
  - The FDA issued a warning : euglycemic diabetic ketoacidosis, Not FDA approved
    -dyspnea, nausea, vomiting, and abdominal pain : Stop

The use of metformin in type 1 diabetes: a systematic review ofefficacy. Diabetologia 2010;**53**:809–820
U.S. Food and Drug Administration:SGLT2 Inhibitors: Drug Safety Communication. Accessed 3 October 2016

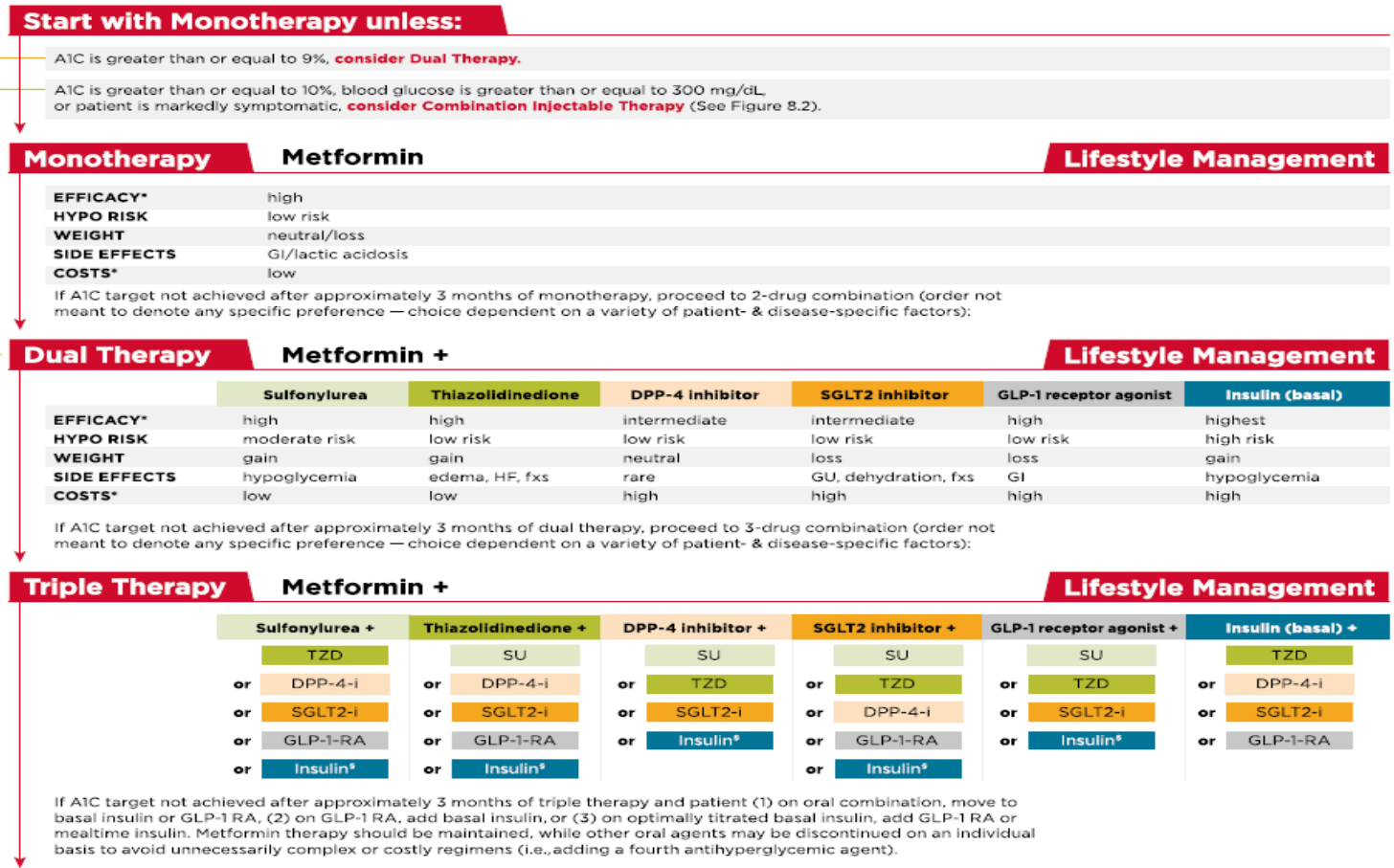
Pharmacologic Therapy for type 2 diabetes

- **Metformin as first-line therapy:** safe, inexpensive, effective
- Risk of cardiovascular events and death ↓
- Safely used in patients with eGFR ≥ 30 mL/min/1.73 m2
- Association with vitamin B12 deficiency

Periodic testing of vitamin B12 levels should be considered – patients with anemia or peripheral neuropathy

Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. **Long-term metformin use and vitamin B12 deficiency** in the Diabetes Prevention Program Outcomes Study. **(DPPOS)** J Clin Endocrinol Metab 2016;101: 1754–1761

Antihyperglycemic therapy in T2DM (ADA2017)



Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy **Metformin** **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy **Metformin +** **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

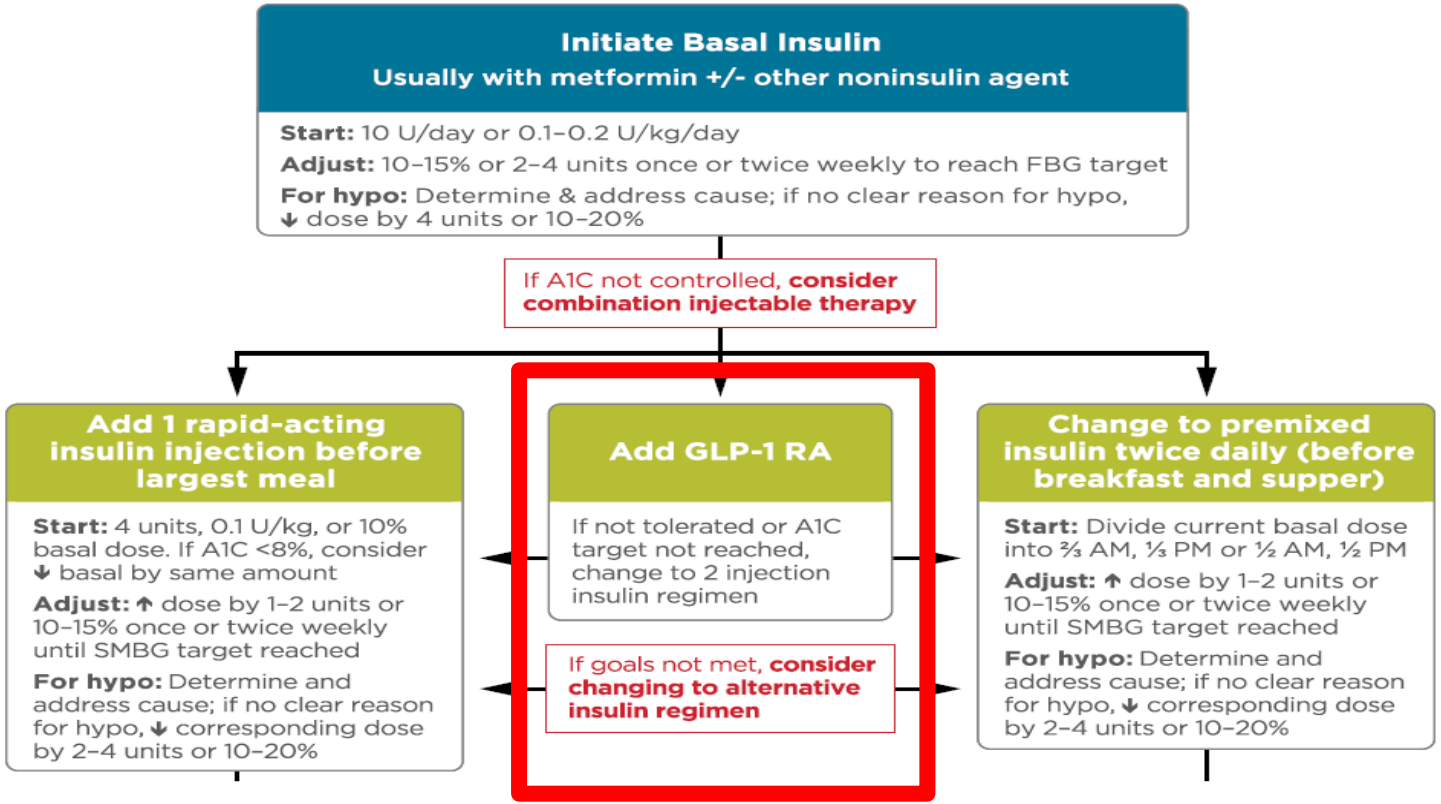
If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy **Metformin +** **Lifestyle Management**

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy



American Diabetes Association Diabetes Care 2017;40:S64-S74

Combination Injectable Therapy

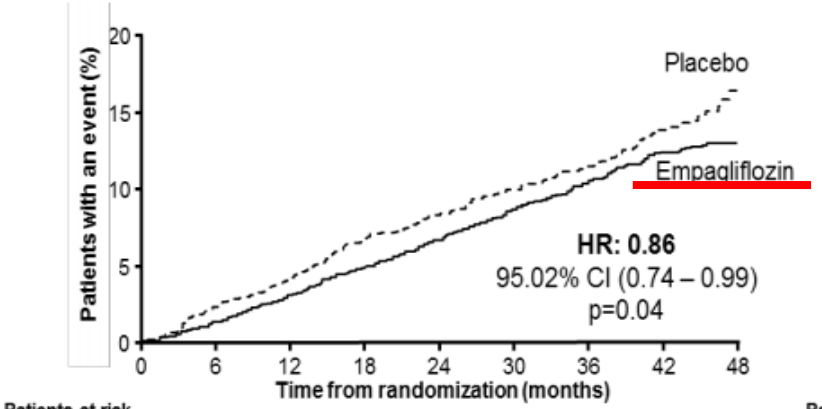
- Studies have demonstrated the noninferiority of
  - Basal insulin + single injection of rapid-acting insulin at the largest meal
  - **Basal insulin plus a GLP-1 receptor agonist**
  - Two daily injections of premixed insulins
- **Basal insulin + GLP-1 receptor agonists**
  - less hypoglycemia
  - weight loss rather than weight gain
  - may be less tolerable
  - have a greater cost

FDA-approved combination products of basal insulin + GLP-1 receptor agonist:
insulin glargine + lixisenatide (Soliqua)
insulin degludec + liraglutide (Xultophy)

Cardiovascular Outcome

EMPA-REG OUTCOME

CV death, non-fatal MI, or non-fatal stroke

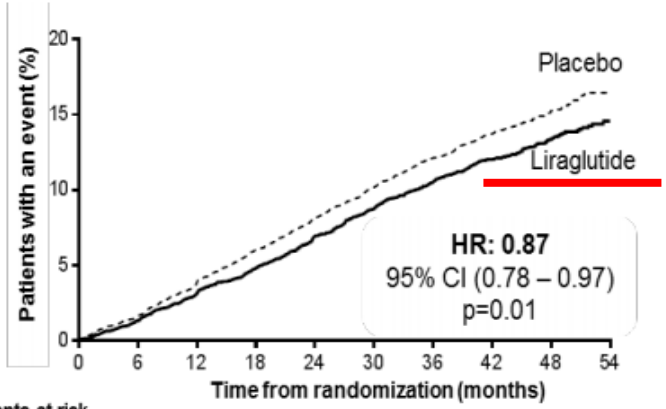


Patients at risk

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

LEADER

CV death, non-fatal MI, or non-fatal stroke



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction. Zinman B et al. N Engl J Med 2015;373:2117-2128.

Empa-Reg: Zinman B et al. N Engl J Med 2015;373:2117-2128. LEADER: Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24.

Take home message

- Metformin : initial pharmacologic agent for the treatment of type 2 diabetes. **A**
- Consider periodic **measurement of vitamin B12 levels** and supplementation
  - anemia or peripheral neuropathy : vitamin B12 levels testing. **B**
- Noninsulin monotherapy at maximum dose not achieve
  - second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin. **A**
- Considerations
  - efficacy, hypoglycemia, impact on weight, side effects, cost, patient preferences. **E**
- Consider **empagliflozin or liraglutide**
  - established cardiovascular disease to reduce the risk of mortality. **B**

Standards of Medical care in diabetes,2017

Patient Education

<u>Thorough patient education is essential regarding:</u>

- **Disease process**
- **Other Risk Factors:**
  - Smoking
  - HTN
  - CAD
- **Self-Care:**
  - Medication
  - Psychological adjustment
  - Nutrition
  - Activity and Exercise
  - Blood-glucose testing
  - Self-administration of insulin or oral drugs
- **Potential complications**
  - How to recognize and treat hypoglycemia and hyperglycemia

경청해주셔서 감사합니다.