


Oral therapies in T2 diabetes

Dr Gary Kilov

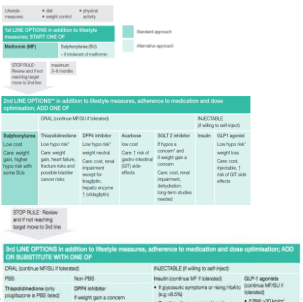
T2D Guidelines - What's New?
What comes after metformin?



Part 1

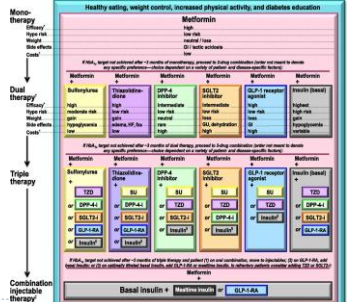
▶ **T2D Guidelines**

RACGP guidelines 2014/15



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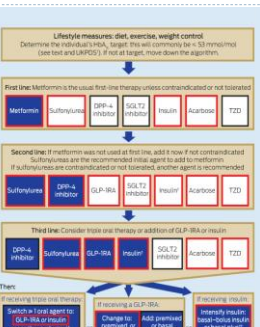
ADA-EASD: Anti-Hyperglycaemic therapy 2015



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American Diabetes Association

ADS guidelines 2015



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Part 2

▶ **What comes after metformin?**

Current RACGP guidelines: Lifestyle measures and 1st line options

Lifestyle measures: • diet • physical activity
• weight control

1st LINE OPTIONS in addition to lifestyle measures: **ADD ONE OF**

- Standard approach: Metformin
- Alternative approach: Sulphonylurea (SU) - if intolerant of metformin

STOP RULE*
Review and if not reaching target move to 2nd line
maximum 3-6 months

*STOP RULE: If BG targets not being attained after max. of 6 months, despite adequate titration doses, STOP and check health literacy, review adherence and exclude occult infection, concurrent meds and consider alternate diagnosis.

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General practice management of type 2 diabetes - 2014-15, Melbourne: The Royal Australian College of General Practitioners and Diabetes Australia, 2014.

Current RACGP guidelines: Lifestyle measures and 2nd line options

2nd LINE OPTIONS** in addition to lifestyle measures, adherence to medication and dose optimisation; **ADD ONE OF**

ORAL (continue MF/SU if tolerated)				INJECTABLE (if willing to self-inject)	
Sulphonylurea Low cost *Pseudo-tumor	Thiazolidinedione Low hypo risk* *Pseudo-tumor	DPP4 inhibitor Low hypo risk* weight neutral	Acarbose low cost *Pseudo-tumor, risk of	SGLT 2 inhibitor low cost if hypoa and *concomitant*	Insulin GLP1 agonist Low hypo risk* weight loss

**Continue medication if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3-6 months.
Refer to individual product PBS listings

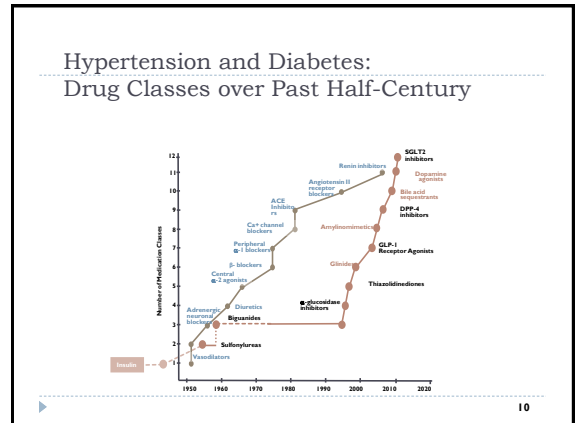
STOP RULE: Review and if not reaching target move to 3rd line

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2nd line agents

▶ *Why is selecting a second line agent so challenging?*

▶



Determinants of selection of 2nd line agents

▶ *Patient Characteristics*

▶ *HbA_{1c} target*

▶ *Characteristics of the pharmacotherapeutic agent*

▶

Determinants of selection of 2nd line agents

▶ *Patient Characteristics*

▶

Considerations in selecting an anti-diabetic medication:

- ▶ **A = Age**
- ▶ **B = Body weight**
- ▶ **C = Complications** (micro and macro-vascular)
- ▶ **D = Duration** of diabetes
- ▶ **E = Life Expectancy**
- ▶ **E = Expense**- can the patient afford it?

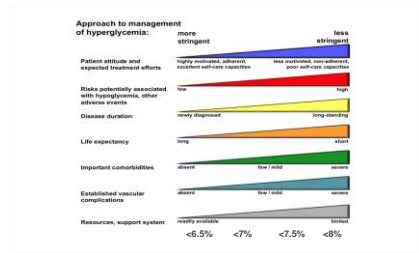
▶ 13 Pathophysiologic Approach to Therapy in Patients With Newly Diagnosed Type 2 Diabetes
RALPH A. DEFRONZO, MD. DIABETES CARE, VOLUME 36, SUPPLEMENT 2, AUGUST 2013

Determinants of selection of 2nd line agents

▶ *HbA_{1c} target*

▶

Selecting an A1C target



▶ 15 Inzucchi S E et al. Dia Care 2015;38:140-149

Set an A_{1c} target

Populations	HbA _{1c}	
	%	SI units
General	≤7%	≤53 mmol/L
Diabetes of short duration and no clinical CVD		
• Requiring lifestyle modification ± metformin	≤6.0%	≤42 mmol/L
• Requiring any antidiabetic agents other than metformin or insulin	≤6.5%	≤48 mmol/L
• Requiring insulin	≤7.0%	≤53 mmol/L
Pregnancy or planning pregnancy	≤6%	≤42 mmol/L
Diabetes of longer duration or clinical CVD (any therapy)	≤7.0%	≤53 mmol/L
Recurrent severe hypoglycaemia or hypoglycaemia unawareness (any therapy)	≤8.0%	≤64 mmol/L
Major co morbidities likely to limit life expectancy (any therapy)	Symptomatic therapy of hypoglycaemia	

▶ Adapted from: Cheung NW, et al. MJA 2009; 191: 339-344; Jones GRD, et al. MJA 2011; 196: 45-46.

Determinants of selection of 2nd line agents

▶ *Characteristics of the pharmacotherapeutic agent*

▶


Selecting a second line agent

- Step 1: Metformin
- Step 2: Efficacy required - A1c drop required
- Step 3: Safety- potentially dangerous adverse effects
- Step 4: Tolerability – potentially unpleasant adverse effects
- Step 5: Affordability – PBS reimbursed or private script
- Step 6: review response

▶

Choosing a 2nd line agents: The new 'class wars'

A CASE STUDY



Case Study

Patient History

- A = Age: 56yrs Taxi driver
- B = Body weight: 98kg (167cm) BMI 35.1
- C = Complications: (microvascular and macrovascular) Nil
- D = Duration of diabetes: 3yrs
- E = Life Expectancy: long
- E = Expense: Can't afford non subsidised meds

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Case Study

Patient History

- BP: 146/84 p. 74
- weight: 98kg (167cm) BMI 35.1
- Meds:
 - Metformin XR 2g nocte
 - Atorvastatin 40/Amlodipine 5 (Caduet) 1 mane
 - Perindopril 10mg 1 mane

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Case Study

Patient History

- A1C: 7.6% (60mmol/mol)
- Chol (Lipids): TC: 3.4; LDL 1.8; Trigs 1.2; HDL 1.0
- U&Es within normal limits, eGFR 87
- LFTs Mild transaminitis

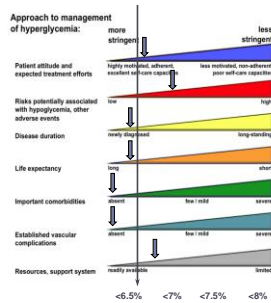
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What is this gentleman's A1C target?
What is the preferred 2nd line agent?



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Considerations in selecting an A1C target



Approach to management of hyperglycemia: more stringent to less stringent

Patient attitude and expected treatment efforts: highly motivated, adherent, excellent self-care capacity to less motivated, non-adherent, poor self-care capacity

Risks potentially associated with hypoglycemia, other adverse events: low to high

Disease duration: newly diagnosed to long-standing

Life expectancy: long to short

Important comorbidities: absent to low/none to severe

Established vascular complications: absent to low/none to severe

Resources, support system: readily available to limited

A1C targets: <6.5%, <7%, <7.5%, <8%

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Selecting a second line agent

Step 1: Metformin

Step 2: Efficacy required - A1c drop required

Step 3: Safety- potentially dangerous adverse effects

Step 4: Tolerability – potentially unpleasant adverse effects

Step 5: Affordability – PBS reimbursed or private script

Step 6: review response

- 56yrs Taxi driver
- Body weight: 98kg (167cm)
- BMI 35.1
- Complications: Nil
- Duration of diabetes: 3yrs
- BP: 146/84 p. 74
- **Meds:**
 - Metformin XR 2g nocte
 - Atorvastatin 40/Amlodipine 5 (Caduet) 1 mane
 - Perindopril 10mg 1 mane
- Δ A1C: 7.6% (60mmol/mol)
- Chol (Lipids): TC: 3.4; LDL 1.8; Trigs 1.2 ; HDL 1.0
- U&Es within normal limits, eGFR 87
- LFTs Mild transaminitis

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Properties of 2nd line agents

Property	SU	TZD	DPP4i	Acarbose	SGLT2i	Insulin	Glp1a
Efficacy required - A1c drop required	+++	+++	++	+	++	++++	+++
Safety- potentially dangerous adverse effects:							
• renal impairment,	++	+++	+++	++	++	+++	++
• CV disease	++	+	+++	+++	+++	+++	+++
• Low risk of drug to drug interactions	++	++	+++	++	++	+++	+++
• Low risk of hypoglycaemia	++	+++	+++	+++	+++	+	+++
Tolerability – Absence of potentially unpleasant adverse effects	++	+	+++	++	++	++	++
Affordability – PBS reimbursed or private script	+++	++	++	+++	++	+++	++

▶

Properties of 2nd line agents

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▶

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• Low risk of drug to drug interactions	++	++	+++	++	++	+++	+++
• Low risk of hypoglycaemia	++	+++	+++	+++	+++	+	+++

▶

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• Low risk of drug to drug interactions	++	++	+++	++	++	+++	+++
• Low risk of hypoglycaemia	++	+++	+++	+++	+++	+	+++
Tolerability – Absence of potentially unpleasant adverse effects	++	+	+++	++	++	++	++

▶

Properties of 2nd line agents

Property	SU	TZD	DPP4i	Acarbose	SGLT2i	Insulin	Glp1a
Efficacy required - A1c drop required	+++	+++	++	+	++	++++	+++
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• renal impairment,	++	+++	+++	++	++	+++	++
• CV disease	++	+	+++	+++	+++	+++	+++
• Low risk of drug to drug interactions	++	++	+++	++	++	+++	+++
• Low risk of hypoglycaemia	++	+++	+++	+++	+++	+	+++
Tolerability – Absence of potentially unpleasant adverse effects	++	+	+++	++	++	++	++
Affordability – PBS reimbursed or private script	+++	++	++	+++	++	+++	++

▶

2nd line options- What's your preference?

2nd LINE OPTIONS** in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF						
ORAL (continue MF/SU if tolerated)					INJECTABLE (if willing to self-inject)	
Sulphonylurea Low cost Care: weight gain, higher hypo risk with some SUs	Thiazolidinedione Low hypo risk* Care: weight gain, heart failure, fracture risks and possible bladder cancer risks	DPP4 inhibitor Low hypo risk* weight neutral Care: cost, renal impairment except for linagliptin, hepatic enzyme ↑ (vildagliptin)	Acarbose low cost Care: ↑ risk of gastro-intestinal (GIT) side-effects	SGLT 2 inhibitor if hypoa concern* and if weight gain a concern Care: cost, renal impairment, dehydration, long-term studies needed	Insulin	GLP1 agonist Low hypo risk* weight loss Care: cost, injectable, ↑ risk of GIT side effects

**Continue medication if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3-6 months. Refer to individual product PBS listings

STCP RLE: Review and if not reaching target move to 3rd line

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2nd line options- My preference

2nd LINE OPTIONS** in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF						
ORAL (continue MF/SU if tolerated)					INJECTABLE (if willing to self-inject)	
Sulphonylurea Low cost Care: weight gain, higher hypo risk with some SUs	Thiazolidinedione Low hypo risk* Care: weight gain, heart failure, fracture risks and possible bladder cancer risks	DPP4 inhibitor Low hypo risk* weight neutral Care: cost, renal impairment except for linagliptin, hepatic enzyme ↑ (vildagliptin)	Acarbose low cost Care: ↑ risk of gastro-intestinal (GIT) side-effects	SGLT 2 inhibitor if hypoa concern* and if weight gain a concern Care: cost, renal impairment, dehydration, long-term studies needed	Insulin	GLP1 agonist Low hypo risk* weight loss Care: cost, injectable, ↑ risk of GIT side effects

**Continue medication if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3-6 months. Refer to individual product PBS listings

STCP RLE: Review and if not reaching target move to 3rd line

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2nd line options- Patient's veto

2nd LINE OPTIONS** in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF						
ORAL (continue MF/SU if tolerated)					INJECTABLE (if willing to self-inject)	
Sulphonylurea Low cost Care: weight gain, higher hypo risk with some SUs	Thiazolidinedione Low hypo risk* Care: weight gain, heart failure, fracture risks and possible bladder cancer risks	DPP4 inhibitor Low hypo risk* weight neutral Care: cost, renal impairment except for linagliptin, hepatic enzyme ↑ (vildagliptin)	Acarbose low cost Care: ↑ risk of gastro-intestinal (GIT) side-effects	SGLT 2 inhibitor if hypoa concern* and if weight gain a concern Care: cost, renal impairment, dehydration, long-term studies needed	Insulin	GLP1 agonist Low hypo risk* weight loss

**Continue medication if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3-6 months. Refer to individual product PBS listings

STCP RLE: Review and if not reaching target move to 3rd line

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2nd line options- Negotiated settlement

2nd LINE OPTIONS** in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF						
ORAL (continue MF/SU if tolerated)					INJECTABLE (if willing to self-inject)	
Sulphonylurea Low cost Care: weight gain, higher hypo risk with some SUs	Thiazolidinedione Low hypo risk* Care: weight gain, heart failure, fracture risks and possible bladder cancer risks	DPP4 inhibitor Low hypo risk* weight neutral Care: cost, renal impairment except for linagliptin, hepatic enzyme ↑ (vildagliptin)	Acarbose low cost Care: ↑ risk of gastro-intestinal (GIT) side-effects	SGLT 2 inhibitor if hypoa concern* and if weight gain a concern Care: cost, renal impairment, dehydration, long-term studies needed	Insulin	GLP1 agonist Low hypo risk* weight loss

**Continue medication if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3-6 months. Refer to individual product PBS listings

STCP RLE: Review and if not reaching target move to 3rd line

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Properties of DPP4is and SGLT2is

Property	DPP4i	SGLT2i
Efficacious	+	++
Durable control	++	++
Well-tolerated	+++	++
• Low risk of hypoglycaemia	+++	++
• Weight neutral or weight loss	+	++
Can be used at all stages of disease	+++	++
Affordability	++	++
Convenient dosing	+++	+++
Simple and painless delivery system	+++	+++
Halts the progression of diabetes	-	-
Safe	++	++
Including patients with renal impairment, CV disease		
Low risk of drug to drug interactions		

▶

Case Study

Clinical Efficacy

• Dapagliflozin (Forxiga) 10mg once daily commenced in addition to Met XR

• Lifestyle modification re-enforced

- Referred to:
 - dietitian
 - exercise physiologist on EPC

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Biochem

Date	12/08/14	30/11/14	Units	Range	δ
HbA _{1c}	7.6 (60)	6.9 (52)	% (mmol/mol)	<6.5 (47.5)	-0.7(8)
Total Cholesterol	3.4	3.5	mmol/L	(below 4.0)	+0.1
Triglycerides	1.2	1.1	mmol/L	(below 2.0)	-0.1
HDL Cholesterol	1.0	1.1	mmol/L	(above 0.9)	-0.19
LDL Cholesterol	1.8	1.9	mmol/L	(below 2.0)	+0.1
Total:HDL ratio	3.4	3.2			

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Biometrics

Biometrics	08/01/14	05/07/14	δ
Weight	98kg	95.6kg	-2.4kg
Height	167cm	167cm	
BMI	35.1	34.3	-0.8
Waist circumference	105cm	103cm	-2cm
BP	146/84	141/80	-5/4
PR	83	81	

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Case Study

Adverse Events

- ~3/12 Post initiation, patient discontinued Forxiga due to pollakiuria.
- Estimated 3 extra voidings per day, 2 at night.
- Very difficult to manage as a taxi driver!

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Case study

Additional Information

- Investigations revealed moderate BPH.
- Patient declined pharmacotherapy for LUTS (Not another pill Doc!)
- Awaiting Urological opinion ?TURP
- Would consider resuming dapagliflozin post resolution of prostatism.
- SGLT2i replaced by DPP4i

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Thank you.



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