Diabetes and the Kidneys

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The views of the speaker are their own and may not represent the opinions of MSD.

T2DM = type 2 diabetes mellitus.

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Speaker Disclosures

MSD

Key educational points

- Attendees will improve their understanding on what Chronic Kidney Disease is, the significance of AKR and eGFR the T2DM treatment options available for renally impaired patients

DPP-4 = dipeptidyl peptidase-4; T2DM = type 2 diabetes mellitus.

1. ADA. *Diabetes Care*. 2017;40(suppl 1):S1–S135. **2.** National Kidney Foundation. *Am J Kidney Dis*. 2007;49(suppl 2):S1–S160.
3. IDF Global Guideline for Type 2 Diabetes 2012. Available at http://www.idf.org/guideline-type-2-diabetes. Accessed March 2017.
4. National Institute for Health and Care Excellence. Chronic Kidney Disease Guidelines. http://www.nice.org.uk/guidance/cg182/evidence/update-full-guideline-191905165. Accessed march 2017.
5. Nauck MA et al. *Diabetes Obes Metab*. 2007;9:194–205. **6.** Arjona Ferreira JC et al. *Diabetes Care*. 2013;36:1067–1073.
7. Arjona Ferreira JC et al. *Am J Kidney Dis*. 2013;61:579–587. **8.** Sitagliptin (JANUVIA) Summary of product characteristics. **9.** Data on File, MSD.

CVD burden in CKD: UK scenario

- Drey *et al, AJKD 2003*
- Southampton population, retrospective study, 1076 Pt with Cr > 150 μmol/lr.
- 5.5 years F/U
- Annual incidence of CKD 0.17%, median survival 35 months
- 4% accepted to RRT, 69% died [46 % died due to CVD]

Age	SMR
16-49	36 fold increase
50-64	12 fold increase
> 65	2 fold increase

Haematuria

- Use reagent strips
- Evaluate further if there is a result of 1+ or more
- Confirm persistent invisible haematuria by two out of three positive sticks
- Check eGFR in all patients
- Do not use urine microscopy to confirm a positive result

Refer to Urology all Patients With

- Visible haematuria (any age)
- Invisible haematuria associated with lower urinary tract symptoms, if infection excluded (any age)
- Asymptomatic invisible haematuria aged > 40 years

Refer to Nephrology

- Patients with rapidly declining renal function (see progressive CKD box)
- Patients with CKD who have had a urological cause excluded
- Patients with ACR > 30

Monitor in Primary Care

- Persistent invisible haematuria without proteinuria follow up annually, repeat testing for haematuria, ACR, eGFR and blood pressure as long as the haematuria persists

eGFR > 60 and ACR < 30	eGFR > 30 and ACR 30 - 69 No haematuria	eGFR > 30 and ACR 30 - 69 With haematuria	eGFR < 30	ACR > 70 Irrespective of eGFR
If no other risk factors for CKD, consider normal. No further action required If risk factors for CKD repeat eGFR in 12 months	See Management of CKD in Primary Care box	See Haematuria box Consider referral for renal specialist opinion	Consider referral for renal specialist opinion	Consider referral for renal specialist opinion unless diabetic on appropriate treatment

Reduce cardiovascular disease risk

- Offer statins for the primary prevention of cardiovascular disease in the same way as in people without CKD
- Use statins for the secondary prevention of cardiovascular disease irrespective of baseline lipids. Use statins in people with diabetes (following NICE/local guidelines)
- Use antiplatelet drugs for the secondary prevention of cardiovascular disease

Progressive CKD

- Define progressive as a decline in eGFR of >5ml/min per year, or >10ml/min in 5 years
  - For a new finding of reduced eGFR, repeat test within 2 weeks to exclude acute renal failure
  - To identify progression take at least 3 eGFRs over at least 90 days
  - Consider whether progression at the observed rate would lead to renal replacement therapy within the person's lifetime
- Chronic use of NSAIDs may be associated with progression; exercise caution and monitor GFR annually in those taking them long-term

In people aged > 70 years, an eGFR in the range 45–59 ml/min, if stable over time and without any other evidence of kidney damage, is unlikely to be associated with CKD-related complications.

Management of CKD in Primary Care

- Optimum blood pressure control
- Use of ACEI/ARBs where indicated
- Reduce cardiovascular disease risk
- Identify progressive CKD
- Offer lifestyle advice – encourage the person to take exercise, achieve a healthy weight and stop smoking
- Refer to community renal dietitian if advice needed for salt, potassium, phosphate, protein and calorie intake
- Medication review – avoid NSAIDs and other nephrotoxic agents

Blood pressure control

- Aim to keep blood pressure below 140/90 mmHg in all patients with CKD (target systolic 120-139)
- Aim to keep BP below 130/80 in people with CKD and diabetes or when the ACR is > 70mg/mmol (target systolic 120-129)

Treatment of Proteinuria

No diabetes

- ACR < 30 mg/mmol and hypertension: offer a choice of antihypertensive treatment (in line with NICE or local guidelines)
- ACR > 30 mg/mmol and hypertension: offer ACEI
- ACR > 70 mg/mmol with or without hypertension: offer ACEI

Diabetes

- ACR > 2.5 (men) with or without hypertension: offer ACEI
- ACR > 3.5 (women) with or without hypertension: offer ACEI

Use of ACEI/ARBs

- Treat with ACEI first; move to ARBs if ACEIs are not tolerated
- Titrate to maximum tolerated dose in all diabetic and non-diabetic patients with proteinuria
- Test eGFR and serum potassium before treatment starts and repeat after 1- 2 weeks and each dose increase
- If eGFR remains stable or shows a small decrease (up to 15%)* continue to titrate dose to maximum
- If eGFR decreases 15 - 25%* following introduction or dose increase:
  - do not modify dose
  - repeat the test after 1 – 2 weeks. Continue to titrate dose if eGFR stable
- If eGFR decreases by more than 25% or plasma creatinine increases more than 30% following ACEI/ARB introduction or dose increase:
  - investigate for other causes of deterioration in renal function, for example volume depletion due to diuretics or NSAIDs
- If no other cause:
  - stop ACEI/ARB therapy or reduce dose to a previously tolerated lower dose
  - add alternative antihypertensive medication if required

Urinary protein concentration and approximate equivalent values

ACR mg/mmol (albumin: creatinine ratio)	PCR mg/mmol (protein: creatinine ration)	Urinary protein excretion (g/24hrs)
30	50	0.5
70	100	1

In established proteinuria (ACR > 30mg/mmol) PCR can be used as an alternative

Potassium

- If serum potassium is significantly increased above the normal reference range
  - do not start ACEI/ARB
  - exclude and treat other factors that promote hyperkalaemia and recheck potassium
- If taking drugs that promote hyperkalaemia, more frequent monitoring of serum potassium may be required
- If serum potassium rises to > 6.0 mmol/l (repeat as soon as possible and exclude haemolysis)* and other drugs that promote hyperkalaemia have been discontinued, stop ACEI/ARBs
- If serum potassium rises to > 7.0 mmol/l refer urgently to the nearest Medical Assessment Unit (MAU) for repeat test and treatment*

Referral to a kidney specialist

- Take into account the individual's wishes and comorbidities when considering referral

Urgent

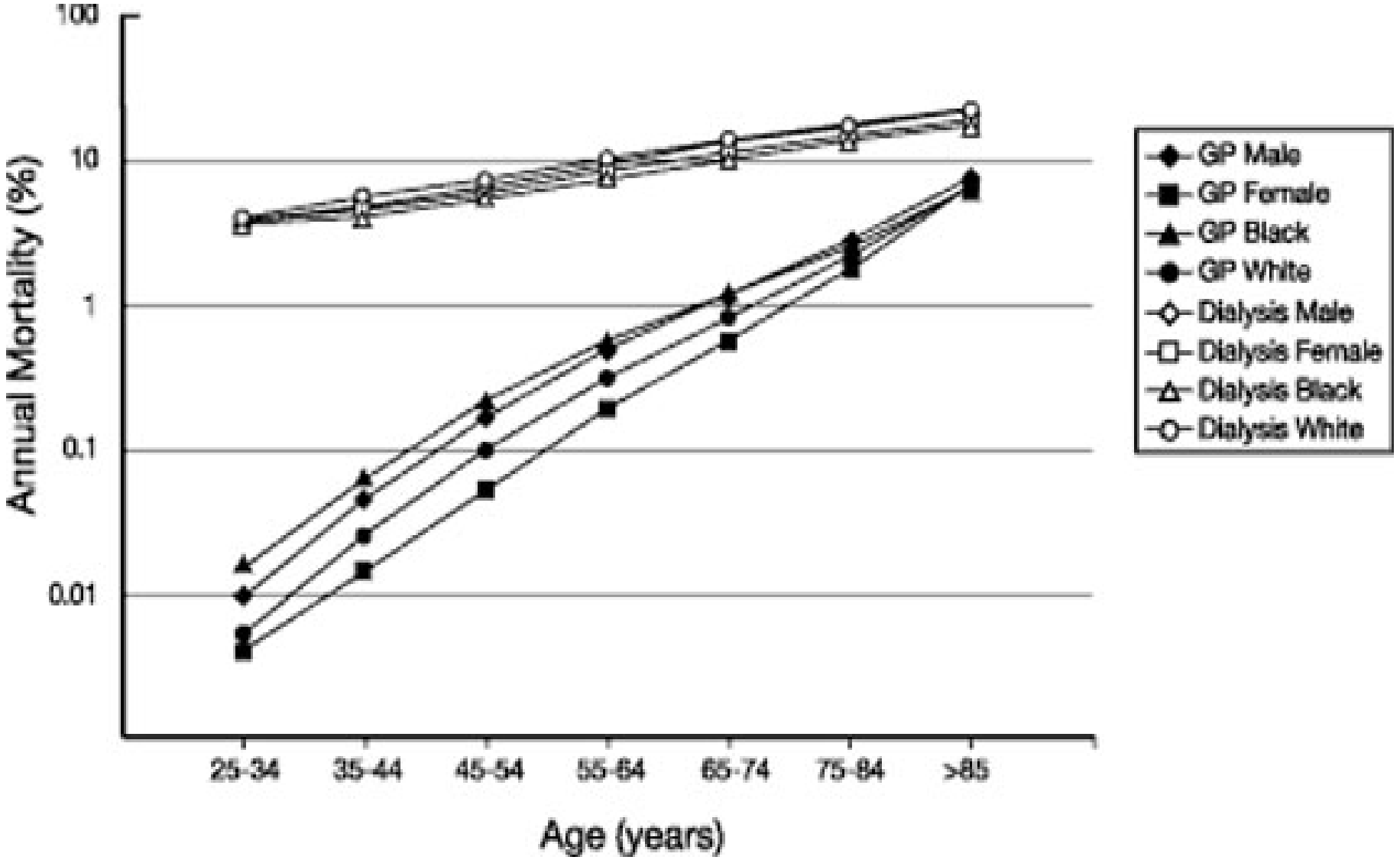
- Suspected Acute Renal Failure
- Newly detected eGFR < 15 ml/min
- Nephrotic Syndrome
- Accelerated Hypertension
- Severe hyperkalaemia (MAU)

Routine

- Stage 4 (eGFR < 30 ml/min) and stable stage 5 CKD (eGFR < 15 ml/min) (with or without diabetes)
- Proteinuria (ACR > 70 mg/mmol) unless known to have diabetes and already appropriately treated
- Proteinuria (ACR > 30 mg/mmol) together with haematuria
- Declining eGFR (> 5 ml/min in 1 year, or > 10 ml/min within 5 years)
- Poorly controlled hypertension despite four antihypertensive drugs at therapeutic doses
- Suspected rare or genetic causes of CKD
- Suspected renal artery stenosis
- Urologically unexplained visible haematuria
- Anaemia Hb < 10.5 g/dl after exclusion of other causes

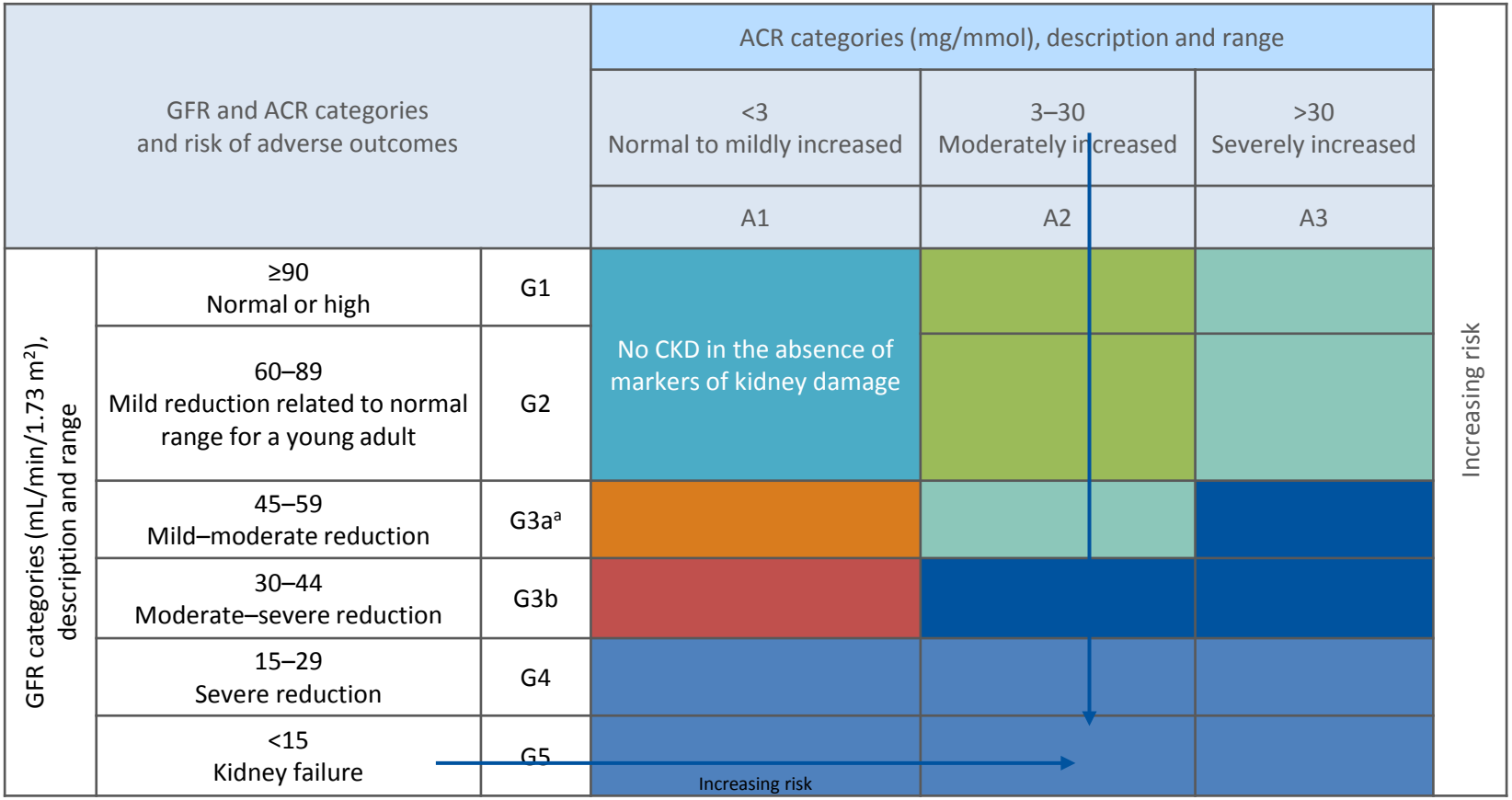
CV Mortality in dialysis population

Foley et al USRDS data



Diagnosis of chronic kidney disease

Classification of chronic kidney disease using GFR and ACR categories[a]



[a]Consider using $eGFR_{cystatinC}$ for people with CKD G3aA1.

Adapted with permission from Kidney Disease: Improving Global Outcomes KDIGO CKD Working Group.[2]

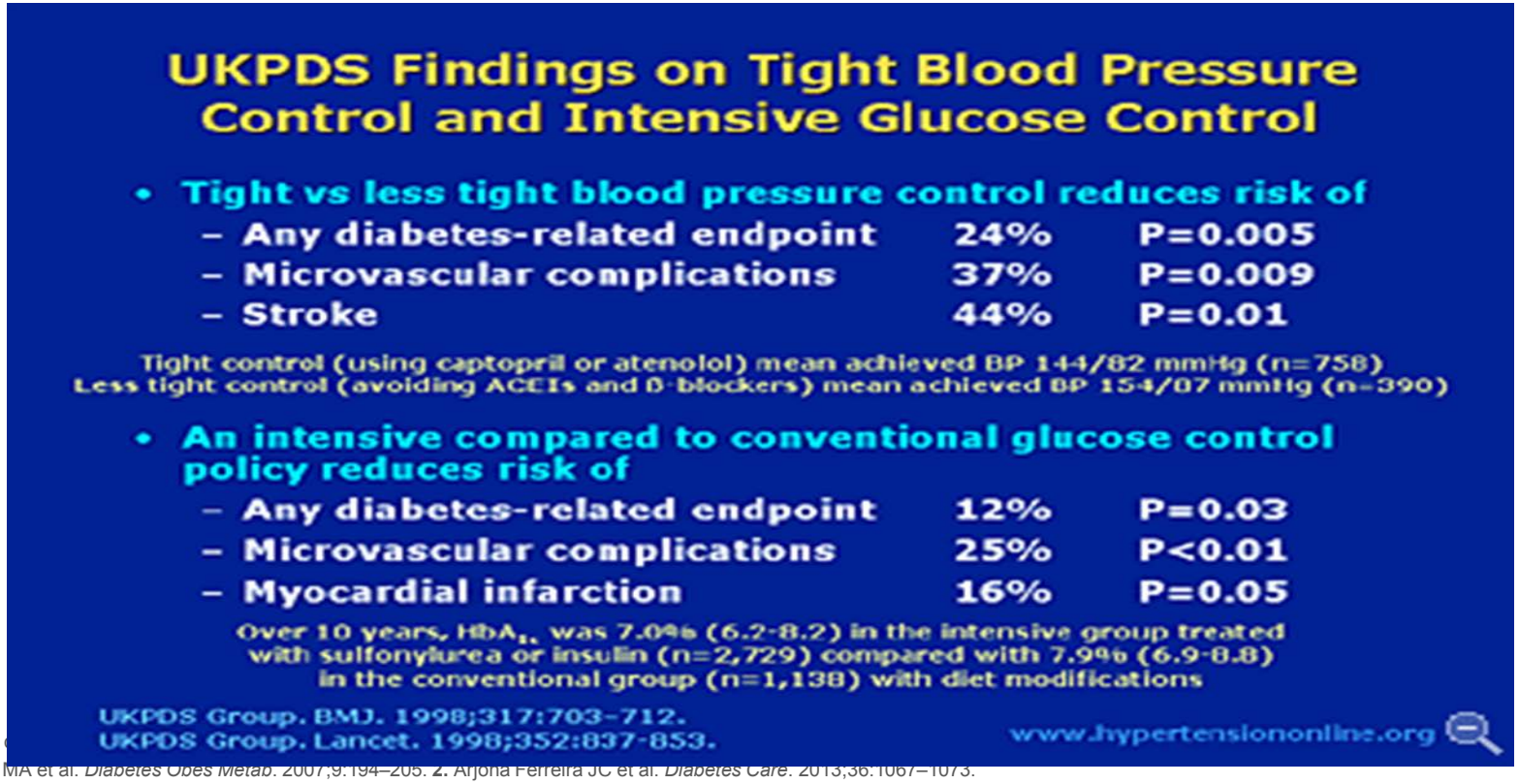
Yellow = Low risk (if no other markers of kidney disease, no CKD). Orange = Moderately increased risk; Green = High risk; Dark Blue = Very high risk.

ACR = albumin:creatinine ratio; CKD = chronic kidney disease; eGFR = estimated GFR; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes.

1. ADA. *Diabetes Care.* 2017;40(suppl 1):S1–S135. **2.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppls.* 2013;3:1–150.

Importance of individualizing treatment for patients

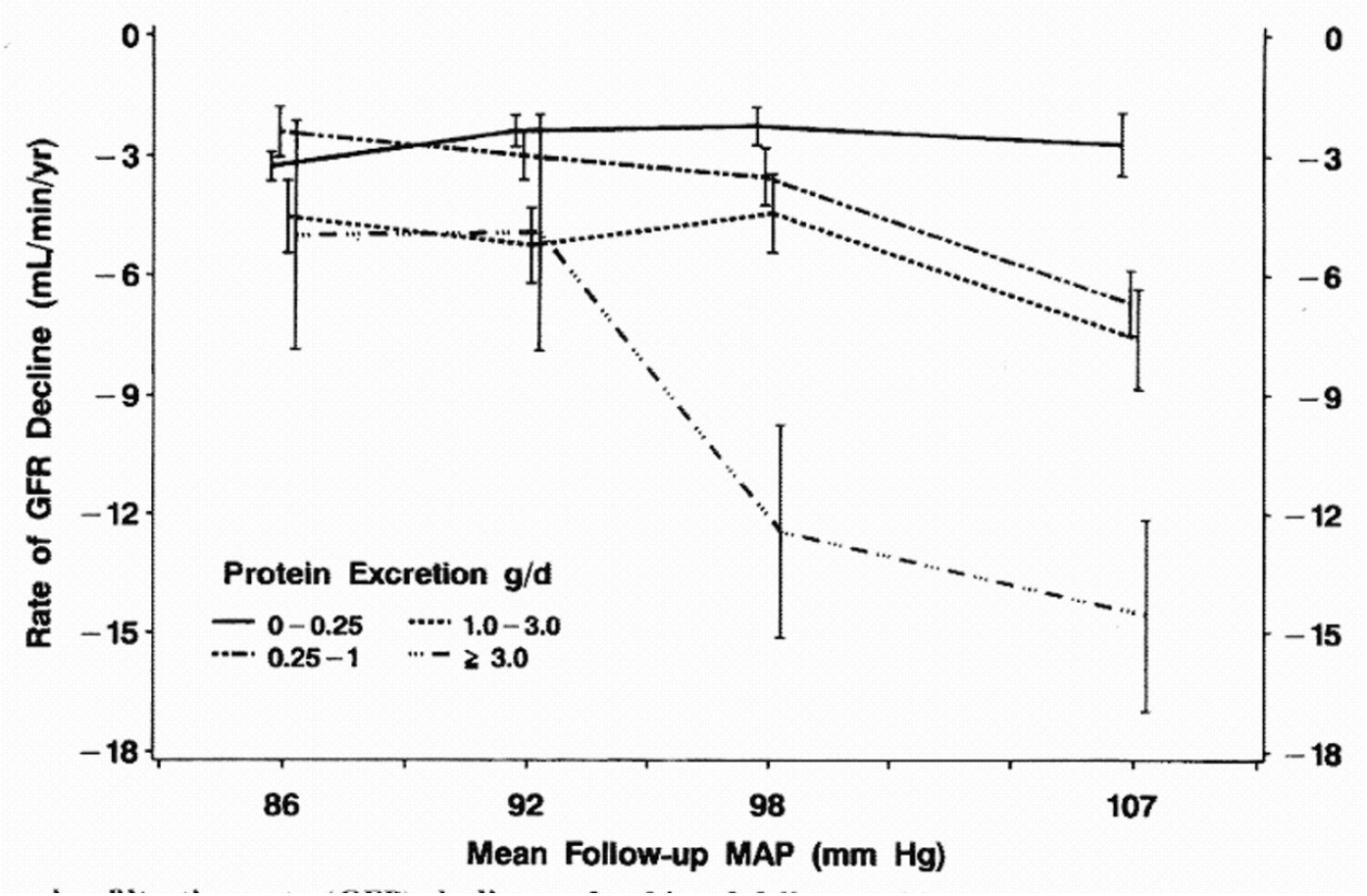
- There are many antidiabetic agents (not including insulin) that are available with differing indications with respect to renal function. They have different data to support these indications and safety profiles, and therefore it is important to individualise treatment in accordance with the summary of product characteristics (SPC) of the agent.
- Within the DPP-4i class, indications and dosages differ with respect to degree of renal impairment.



DPP-4i = d

1. Nauck MA et al. *Diabetes Obes Metab*. 2007;9:194–205. **2.** Arjona Ferreira JC et al. *Diabetes Care*. 2013;36:1067–1073.
3. Arjona Ferreira JC et al. *Am J Kidney Dis*. 2013;61:579–587. **4.** Deacon C et al. *Diabetes Obes Metab*. 2016;18:333–347.

Mean glomerular filtration rate (GFR) decline and achieved follow-up blood pressure in study A. Regression lines relating the estimated mean glomerular filtration rate decline over 3 years to mean follow-up mean arterial pressure (MAP) for groups of patients defined according to baseline proteinuria



Peterson, J. C. et. al. Ann Intern Med 1995;123:754-762

Annals of Internal Medicine

ABCDRA management guidelines

- Sulfonyluria- Risk of hypoglycaemia- CBG monitoring is mandatory. Avoid if GFR<30 ml/min or if on insulin <45 ml/min.
- Meglitinides- Risk of hypo- CBG mandatory.
- SGLT-2: dapagliflozolin GFR>60; Cana and Empa GFR>45 ml/min
- GLP-1 Agonists: Renoprotective and cardio-protective. NOT LICENCED FOR GFR<30 ml/min
- Pioglitazone- risk of fluid retention starts at CKD IV. **NOT SAFE IF HEART FAILURE**. Other risks – hip fracture, bladder malignancy

ABCDRA management guidelines

7 Dipeptidyl peptidase-4 inhibitors

Recommendations

1 We recommend that patients with type 2 diabetes and chronic kidney disease (CKD) of all stages be considered for treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors (Grade 1B).

2 We recommend that doses of all UK licensed DPP-4 inhibitors are appropriately reduced in accordance with the degree of renal impairment (including maintenance haemodialysis (MHDx)) except linagliptin (Grade 1B).

3 Patients with type 2 diabetes and CKD can be safely prescribed DPP-4 inhibitors without the risk of hypoglycaemia or weight gain at all stages of renal disease (Grade 1B).

4 There are no current data to recommend the use of DPP-4 inhibitors specifically to lower albuminuria in patients with type 2 diabetes and CKD (Grade 1C).

5 There are no current data to suggest that DPP-4 inhibitors (except saxagliptin) are associated with an excess risk of hospitalisation for patients with heart failure, type 2 diabetes and CKD (Grade 1A).

Type 2 diabetic antihyperglycaemic agents and renal function (using creatinine clearance)

		CKD stage	Mild	Moderate	Severe	ESRD	ESRD (dialysis)
		CrCl (mL/min)	50–80	30–50	<30		
Class	Drug						
Sulfonylureas	Glicazide (DIAMICRON)[1]		**DOSE:** 40–320 mg daily in divided doses[1]				
	Glibenclamide (GLIBENCLAMIDE)[2]		**DOSE:** Dose reduction and careful patient monitoring may be needed[2]				
	Glipizide (MINODIAB)[3]		Pharmacokinetics and/or pharmacodynamics of glipizide may be affected[3]				
	Tolbutamide (TOLBUTAMIDE)[4]		**DOSE:** 500–1500 mg. Start with lower doses; carefully monitor blood glucose levels[4]				
DPP-4i	Alogliptin (VIPIDIA▼)[5]		No dose adjustment: 25 mg once daily[5]	**DOSE:** dose reduction to **12.5** mg once daily[5]	**DOSE:** dose reduction to 12.5 mg once daily[5]	**DOSE:** dose reduction to 6.25 mg once daily[5]	
	Linagliptin (TRAJENTA)[6]		No dose adjustment: 5 mg once daily[6]				
	Saxaglitpin (ONGLYZA)[7]		No dose adjustment: 5 mg once daily[7]	**DOSE:** dose reduction to 2.5 mg once daily[7]			
	Sitagliptin (JANUVIA)[8]		See next slide				
Thiazolidinediones	Pioglitazone (ACTOS)[9]		No dose adjustment: 15–45 mg once daily[9]				
GLP1-receptor agonists	Lixisenatide (LYXUMIA)[10]		No dose adjustment: initially 10 µg once daily for 14 days, then increased to 20 µg once daily. Dose to be taken within 1 hour before the first meal of the day or the evening meal[10]				
	Liraglutide (VICTOZA)[11]		No dose adjustment: 0.6–1.8 mg once daily[11]				
	Exenatide (BYDUREON)[12]		No dose adjustment: 2 mg once weekly[12]				

No dose adjustment

Use with caution/dose reduction

Contraindicated

CKD = chronic kidney disease; CrCl = creatinine clearance; DPP-4i = dipeptidyl dipeptidase-4 inhibitor; ESRD = end-stage renal disease; GLP1 = glucagon-like peptide 1; SPC = summary of product characteristics.

1. Gliclazide (DIAMICRON) SPC. **2.** Glibenclamide (GLIBENCLAMIDE) SPC **3.** Glipizide (MINODIAB) SPC.. **4.** Tolbutamide (TOLBUTAMIDE) SPC **5.** Alogliptin (VIPIDIA) SPC.. **6.** Linagliptin (TRAJENTA) SPC. **7.** Saxagliptin (ONGLYZA) SPC.. **9.** Pioglitazone (ACTOS) SPC. **10.** Lixisenatide (LYXUMIA) SPC.**11.** Liraglutide (VICTOZA) SPC. **12.** Exenatide (BYDUREON) SPC.

Antihyperglycaemic agents and renal function (using GFR)

		CKD stage	1	2	3a	3b	4	5
		GFR (mL/min/)	>90	60–89	45–59	30–44	15–29	<15
		Terms	Normal–high	Mildly decreased	Mildly–moderately decreased	Moderately–severely decreased	Severely decreased	Kidney failure
Class	Drug							
DPP-4i	Sitagliptin (JANUVIA)		No dose adjustment:100 mg once daily [6]	No dose adjustment:100 mg once daily [6]	No dose adjustment:100 mg once daily [6]	**DOSE:** dose reduction to 50 mg once daily [6]	**DOSE**: dose reduction to 25 mg once daily [6]	**DOSE:** dose reduction to 25 mg once daily [6]
Biguanides	Metformin (GLUCOPHAGE)[1]		No dose adjustment needed: maximum of 3 g daily in divided doses[1]		**DOSE:** dose reduction to a maximum of 2 g once daily in divided doses[1]	**DOSE:** dose reduction to a maximum of 1 g once daily in divided doses[1]		
GLP1-receptor agonists	Albiglutide (EPERZAN▼)[2]		No dose adjustment needed: 30 mg once weekly; dose may be increased to 50 mg once weekly based on glycaemic response[2]					
SGLT2 inhibitors	Canagliflozin (INVOKANA▼)[3]		No dose adjustment needed: 100–300 mg once daily.[3]		eGFR <60 mL/min/1.73 m^2: Do not initiate treatment. If patient is already on treatment, reduce dose to 100 mg once daily.[3]			
	Dapagliflozin (FORXIGA)[4]		No dose adjustment needed: 10 mg once daily[4]					
	Empagliflozin (JARDIANCE▼)[5]		No dose adjustment: 10 mg once daily, can be increased to 25 mg once daily if tighter glycaemic control is needed.[5]		eGFR <60 mL/min/1.73 m^2: Do not initiate treatment. If patient is already on treatment, reduce dose to 10 mg once daily.[5]			

No dose adjustment

Use with caution/dose reduce

Contraindicated

CKD = chronic kidney disease; eGFR = estimated glormerular filtration rate; GLP1 = glucagon-like peptide 1; SGLT2 = sodium glucose co-transporter 2; SPC = summary of product characteristics.

1. Metformin (GLUCOPHAGE) SPC. **2.** Albiglutide (EPERZAN) SPC. **3.** Canagliflozin (INVOKANA) SPC.. **4.** Dapagliflozin (FORXIGA) SPC. **5.** Empagliflozin (JARDIANCE) SPC. 6. Sitagliptin (JANUVIA) SPC

NICE recommendation for metformin[1]

In adults with type 2 diabetes:

- Review dose of metformin if the eGFR <45 mL/min/1.73 m^2: summary of product characteristics for metformin states a maximum dose in this case[2]
- Stop metformin if the eGFR <30 mL/min/1.73 m^2
- Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 mL/min/1.73 m^2

eGFR = estimated glomerular filtration rate.

1. NICE guidelines [NG28] Type 2 diabetes in adults: management. Published December 2015.

2. Metformin (Glucophage) summary of product characteristics.

Sitagliptin in renal impairment

Degree of renal impairment in GFR	Sitagliptin[1]
Mild GFR ≥ 60 to <90 ml/min	100 mg OD
Moderate GFR ≥ 45 to <60 ml/min	100 mg OD
Moderate GFR ≥ 30 to <45 mL/min	50 mg OD
Severe GFR ≥15 to <30 mL/min	25 mg OD
ESRD GFR <15 mL/min	25 mg OD

OD = once daily; SPC = summary of product characteristics. ESRD: End Stage Renal Disease

1. Sitagliptin (Januvia) Summary of product characteristics.

DPP-4 inhibitors in renal impairment

Degree of renal impairment in CrCl	Saxagliptin[1`]	Linagliptin[2]	Vildagliptin[3]	Alogliptin ▼[4]
Mild CrCl ≥50 mL/min	5 mg	5 mg	50 mg BD	25 mg
Moderate CrCl ≥30 to <50 mL/min	2.5 mg	5 mg	50 mg BD	12.5 mg
Severe CrCl <30 mL/min	2.5 mg	5 mg	50 mg OD	12.5 mg
ESRD	Not recommended in ESRD requiring haemodialysis	5 mg	50 mg OD with caution	6.25 mg Experience in patients requiring renal dialysis is limited

BD = twice daily; CrCl = creatinine clearance; ESRD = end-stage renal disease. ; OD = once daily; SPC = summary of product characteristics.

1. Saxagliptin (Onglyza) Summary of product characteristics. **2.** Linagliptin (Trajenta) Summary of product characteristics. **3.** Vildagliptin (Galvus) Summary of product characteristics. **4.** Alogliptin (Vipidia) Summary of product characteristics.

Exposure of DPP-4 inhibitors in patients with renal impairment[1–7]

Exposure in patients with renal impairment

	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin ▼	Linagliptin
Mild renal impairment	✓	✓	✓	✓	✓
Moderate renal impairment	✓	✓	✓	✓	✓
Severe renal impairment	✓	✓	✓	✓	✓
End-stage renal disease	✓	✓	✓	✓	✓
Completed CV safety trial	✓	✓	✓	✓	☐[a]
Completed renal sub-analysis	✓		✓		

[a]CARMELINA: Cardiovascular and Renal Micovascular Outcome Study with Linagliptin with Patients with Type 2 Diabetes Mellitus. Completion date of January 2018.

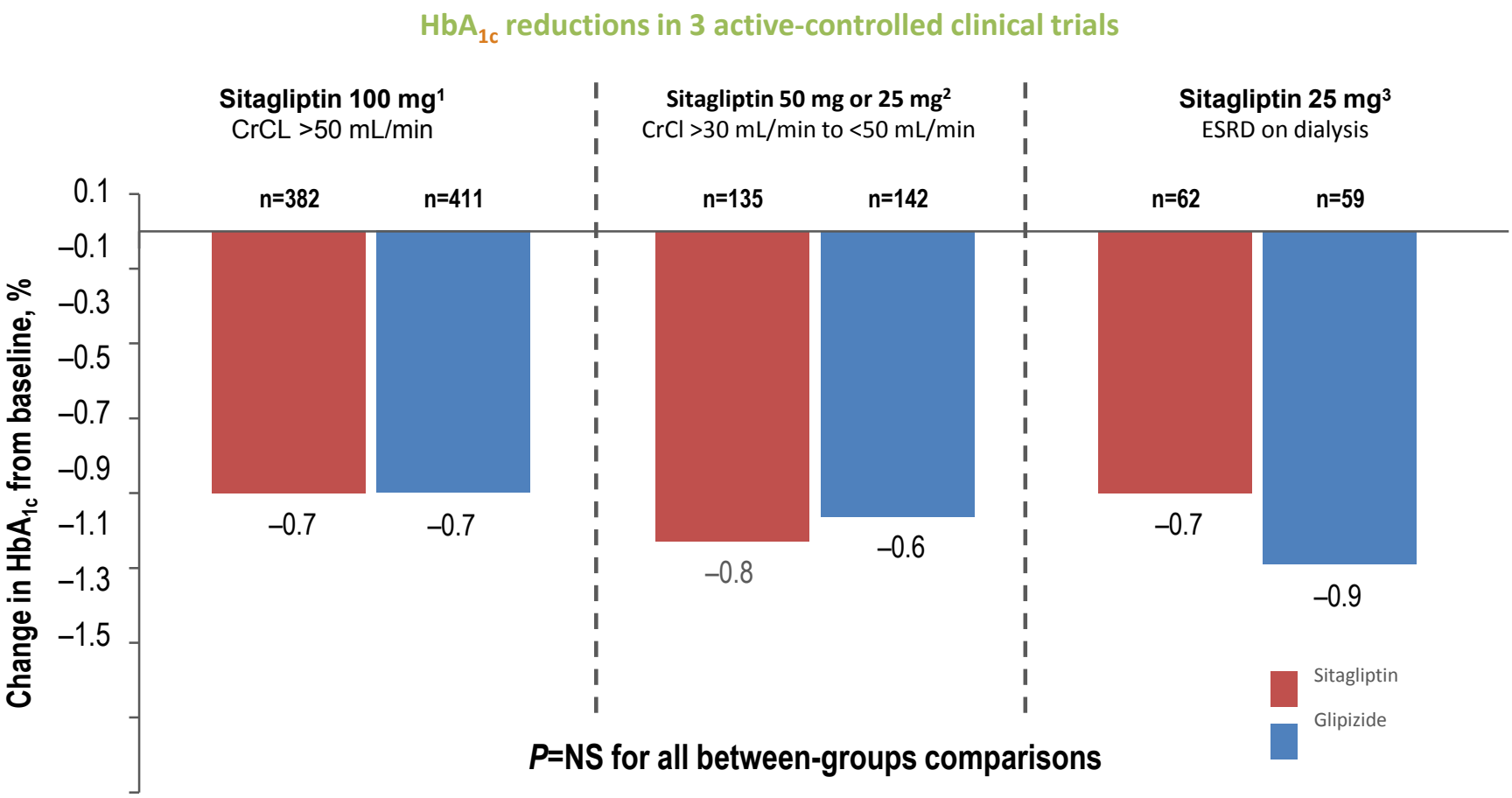
DPP-4 = dipeptidyl peptidase-4; CV = cardiovascular; SPC = summary of product characteristics.

1. Sitagliptin (Januvia) SPC. **2.** Saxagliptin (Onglyza) SPC. **3.** Linagliptin (Trajenta) SPC. **4.** Vildagliptin (Galvus) SPC. **5.** Alogliptin (Vipidia) SPC.
6. Cornel JH et al. *Diabetes Care*. 2016;39:2304–2310.
7. Mosenzon O et al. *Diabetes Care*. 2016;39: S146-S153

There is no loss of sitagliptin efficacy at reduced doses according to renal function

Please refer to the Sitagliptin SPC for dose adjustments in renal impairment.

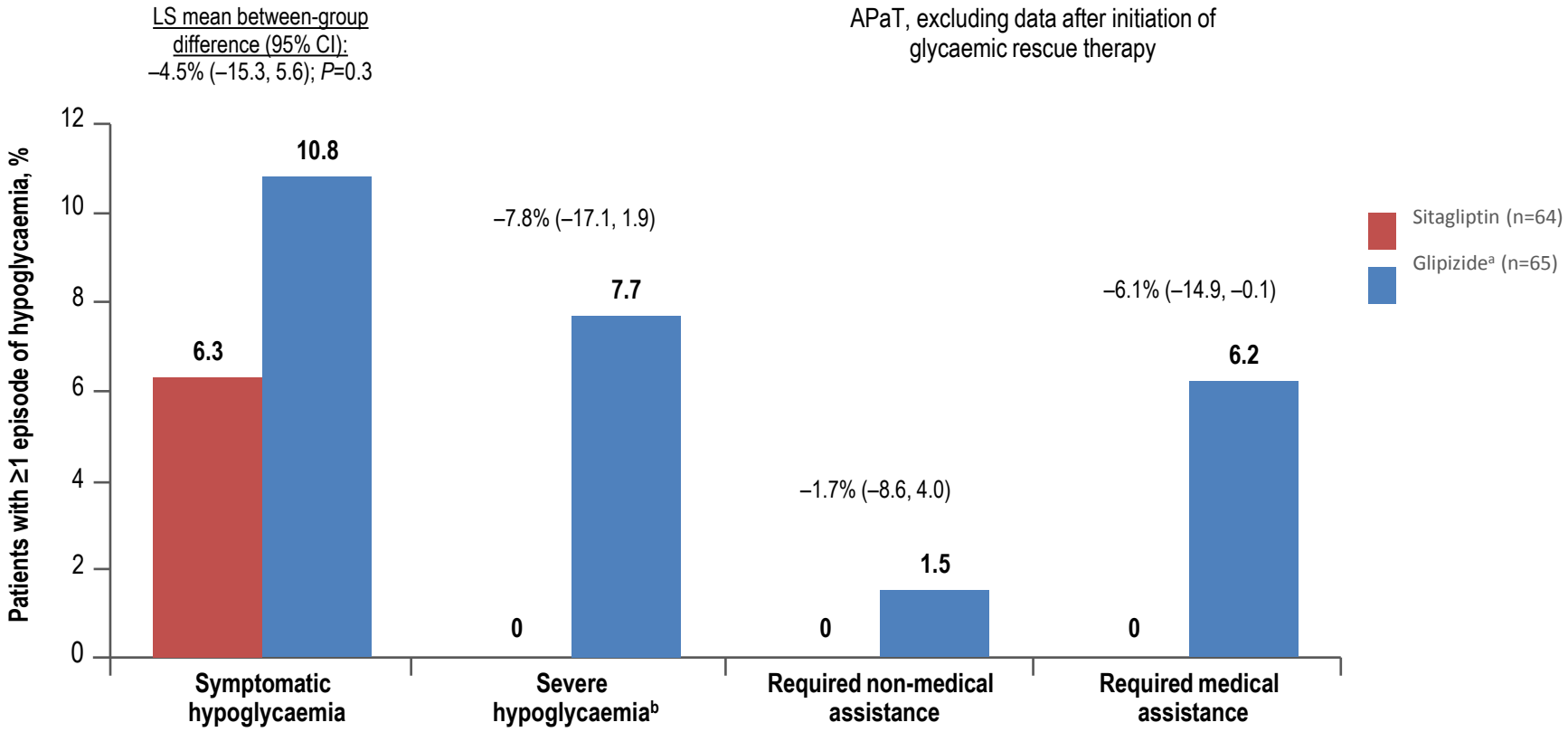
Please note that the data below is from 3 different studies. These studies cannot be compared as they are conducted in different patient populations



ESRD = end-stage renal disease; SPC = summary of product characteristics. CrCl: Creatinine Clearance

1. Nauck MA et al. *Diabetes Obes Metab*. 2007;9:194–205. **2.** Arjona Ferreira JC et al. *Diabetes Care*. 2013;36:1067–1073. **3.** Arjona Ferreira JC et al. *Am J Kidney Dis*. 2013;61:579–587.

Hypoglycaemia Risk with Sitagliptin[1]

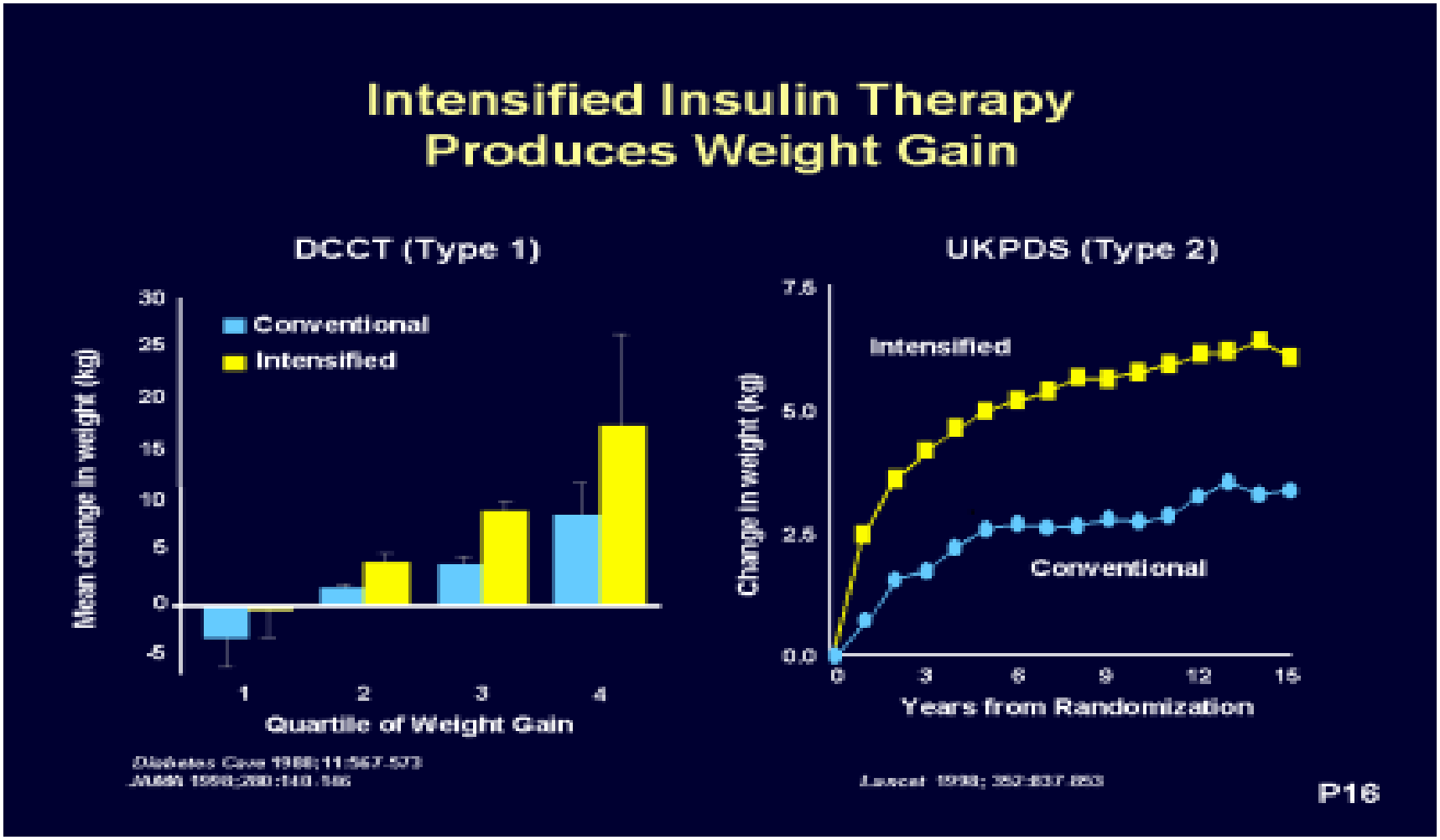


[a]Mean dose of glipizide was 5.3 mg per day.
[b]Events of hypoglycaemia requiring (non-medical) assistance of others, requiring medical intervention, or exhibiting markedly depressed level of consciousness, loss of consciousness, or seizure were considered severe.

APaT = All patients as treated; CI = confidence interval; LS = least squares.

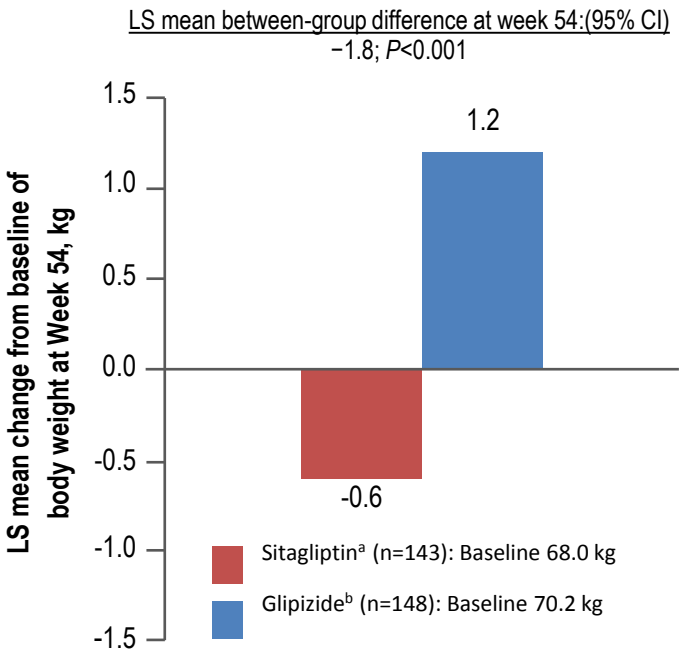
1. Arjona Ferreira JC et al. *Am J Kidney Dis*. 2013;61(4):579–587.

Tight glycaemic control can lead to weight gain

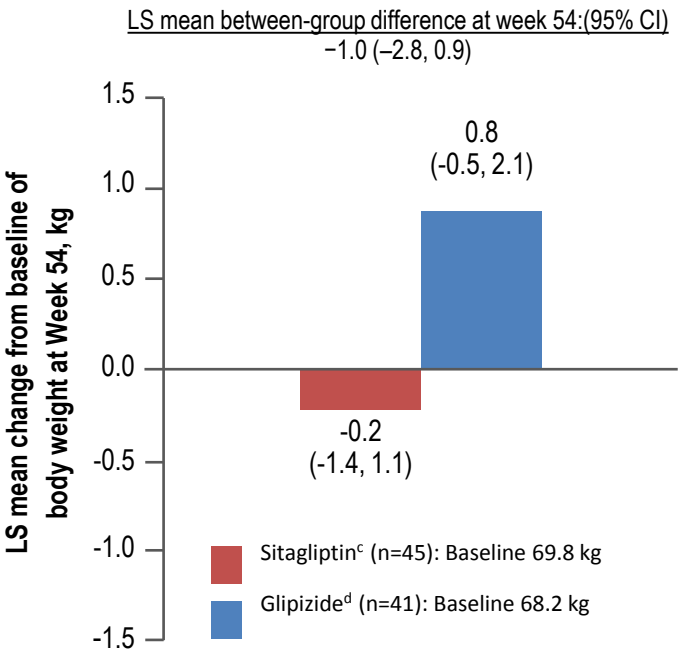


Weight gain in patients with T2DM and moderate-to-severe chronic renal insufficiency or ESRD on dialysis[1,2]

Moderate-to-severe renal impairment (per protocol population)



ESRD on dialysis (APaT, excluding data after initiation of glycaemic rescue therapy)



Adapted with permission from Arjona Ferreira JC.[1]

[a]25 mg once daily or 50 mg once daily. [b]Mean dose of glipizide was 7.7 mg per day. Glipizide was initiated at 2.5 mg/day and titrated to a maximum of 20 mg/day.
[c]25 mg once daily. [d]Mean dose of glipizide was 5.3 mg per day. Glipizide was initiated at 2.5 mg/day and titrated to a maximum of 20 mg/day.

APaT = All patients as treated; CI = confidence interval; ESRD = end-stage renal disease; LS = least squares; T2DM = type 2 diabetes mellitus.

1. Arjona Ferreira JC et al. *Diabetes Care*. 2013;36:1067–1073. **2.** Arjona Ferreira JC et al. *Am J Kidney Dis*. 2013;61:579–587.

Most DPP-4 inhibitors are currently studied in large CV outcome trials

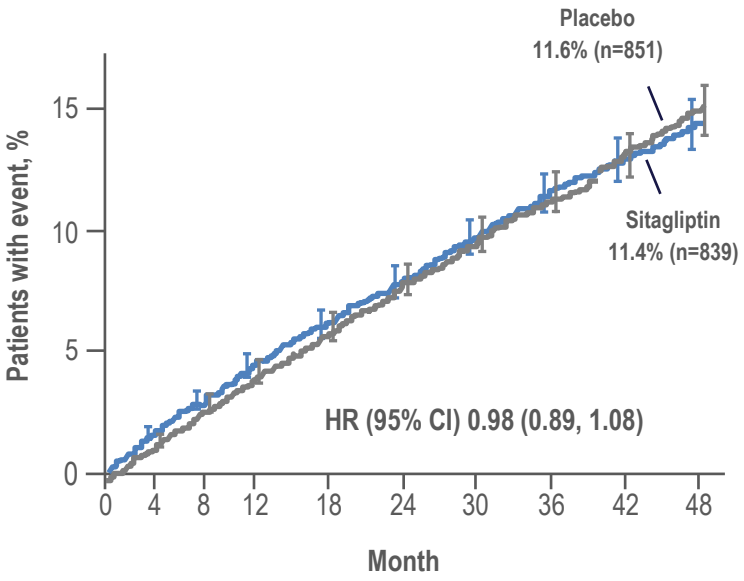
	TECOS[1]	SAVOR-TIMI 53[2]	EXAMINE[3]	VIVIDD[4]	CARMELINA[5]	CAROLINA[6]
DPP-4 inhibitor	JANUVIA	Saxagliptin	Alogliptin▼	Vildagliptin	Linagliptin	Linagliptin
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
No. of patients	14,671	16,492	5,380	798	8,300	6,000
Trial completion	March 2015	May 2013	June 2013	August 2012	estimated January 2018	estimated March 2019
Background diabetes therapy per protocol	Any	Any	Any	Any	Any	Predominantly on metformin background
Median duration of follow-up (years)	3.0	2.1	1.5	1		
Key inclusion criteria	Pre-existing CV disease	High risk for CV events	History of ACS	Patients with T2DM, diagnosed at least 3 months prior to Visit 1, CHF (NYHA Class I, Class II, or Class III) at Visit 1, LVEF < 40%	Previous vascular complications and albuminuria; evidence of renal-related end-organ damage	Previous vascular complications; evidence of end-organ damage; ≥2 specified traditional CV risk factors

1,4,5. Primary end point: CV death, non-fatal MI, non-fatal stroke, hospitalisation due to unstable angina pectoris.
2, 3. Primary end point: major adverse CV events (CV death, non-fatal MI, non-fatal stroke).
CV = cardiovascular; MI = myocardial infarction.

1. Green JB et al. *N Engl J Med*. 2015;373:232–242.
2. Scirica BM et al. *N Engl J Med*. 2013;369:1317–1326.
3. White WB et al. N Engl J Med. 2013;369:1327–1335.
4. McMurray J., et al JACC 2017
5. Clinical trials 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT01897532?term=carmelina&rank=1.
6. Clinical trials 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT01243424?term=carolina&cond=diabetes&titles=carolina&rank=1.

TECOS CV safety trial: primary composite CV outcome and hospitalisations for heart failure (ITT)[1]

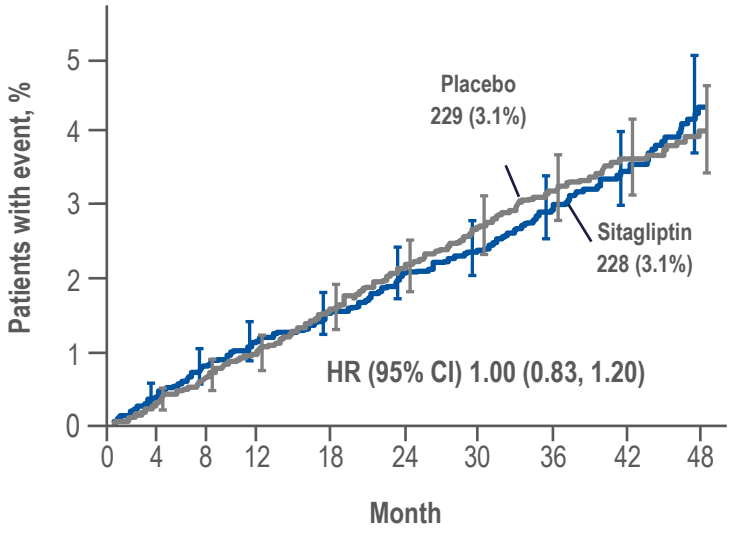
Primary composite CV outcome: ITT population



Between-group difference (ITT) was not statistically significant for superiority: *P*=0.65

Between-group difference (PP) was statistically significant for non-inferiority: *P*<0.001[a]

Hospitalisations for heart failure: ITT population



Between group difference was not statistically significant: *P*=0.98

Adapted with permission from Green JB et al.[1]

[a]Non-inferiority *P*-value for a margin of 1.30 in hazard ratio.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention-to-treat; PP = per protocol; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

1. Green JB et al. *N Engl J Med*. 2015;373:232–242.

TECOS CV safety trial: key non-CV outcomes and serious adverse events (ITT)[1]

Non-CV outcomes[a] n (%); rate per 100 patient-years	Sitagliptin (n=210)	Placebo (n=7339)	HR (95% CI)	*P*-value
Acute pancreatitis	23 (0.3); 0.11	12 (0.2); 0.06	1.93 (0.96, 3.88)	0.07
Charter-defined cancer	268 (3.7); 1.25	290 (4.0); 1.37	0.91 (0.77, 1.08)	0.27
Pancreatic cancer	9 (0.1); 0.04	14 (0.2); 0.07	0.66 (0.28, 1.51)	0.32
Severe hypoglycaemia	160 (2.2); 0.78	143 (1.9); 0.70	1.12 (0.89, 1.40)	0.33

All patients as treated excluding data after initiation of glycaemic rescue therapy

Serious adverse events	Sitagliptin (n=7332)		Placebo (n=7339)	
	Patients; n (%)	Events	Patients; n (%)	Events
Benign, malignant or unspecified neoplasms	341 (4.7)	405	371 (5.1)	470
Injury, poisoning, or procedural complications	146 (2.0)	165	133 (1.8)	153
Gastrointestinal disorder	130 (1.8)	143	102 (1.4)	121
Musculoskeletal and connective-tissue disorders	118 (1.6)	136	93 (1.3)	102
Respiratory, thoracic, or mediastinal disorders	66 (0.9)	81	77 (1.0)	95

Adapted with permission from Green JB et al.[1]
[a]ITT population.
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention-to-treat; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

1. Green JB et al. *N Engl J Med*. 2015;373:232–242.

Oral anti-diabetic therapy : DPP-4i licensed indications

		sitagliptin[1]	vildagliptin[2]	saxagliptin[3]	linagliptin[4]	alogliptin[5] ▼
Monotherapy (oral)	If metformin is contraindicated or not tolerated	✓	✓	✓	✓	✗
Dual therapy (oral)	Add on to metformin	✓	✓	✓	✓	✓
	Add on to SU	✓	✓	✓	✗	✓
	Add on to TZD	✓	✓	✓	✗	✓
Triple therapy (oral)	Add on to metformin + SU	✓	✓	✓	✓	✗[a]
	Add on to metformin + TZD	✓	✗[a]	✗[a]	✗	✓
	Add on to metformin + SGLT2i	✗	✗	✓[b]	✓[c]	✗

If you are currently using metformin + any DPP-4i, a SGLT2i can be added in third line in line with the SPCs for all SGLT2is [6-8]

KEY
a-Safety and efficacy has not been established.
b- In combination with dapagliflozin.
c- In combination with empagliflozin.

For combination therapy with insulin, please refer to individual SPCs

1. Sitagliptin SPC 2. Vildagliptin SPC 3. Saxagliptin SPC. 4. Linagliptin SPC. 5. Alogliptin SPC . **6.** Canagliflozin SPC. **7.** Dapagliflozin SPC. 8. Empagliflozin SPC.

Sitagliptin: use in special populations[1]

Administration	Sitagliptin[1] Once daily
Mild or moderate hepatic impairment	✓
Severe hepatic impairment	✓
Mild or moderate renal impairment	✓[a]
Severe renal impairment	✓[a]
ESRD/haemodialysis	✓[a]
>65 years	✓

✓ = No clinical experience, care should be exercised

[a]Dose adjustment for patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring peritoneal dialysis or hemodialysis.

1. Sitagliptin Summary of product characteristics.

Summary

- Chronic kidney disease is a recognised comorbidity among patients with T2DM[1,2]
- Guidelines support ongoing assessment of renal function and management of chronic kidney disease in patients with T2DM[3–6]
- The presence of renal insufficiency is an important consideration for choice of antihyperglycaemic therapy[7]
- DPP-4 inhibitors may be an appropriate choice for patients with T2DM and renal impairment[8]

DPP-4 = dipeptidyl peptidase-4; T2DM = type 2 diabetes mellitus.

1. Afkarian M et al. *J Am Med Assoc*. 2016;316:602–610. **2.** Bailey RA et al. *BMC Research Notes*. 2014;7:415.
3. American Diabetes Association (ADA). *Diabetes Care*. 2017;40(suppl 1):S1–S135. **4.** National Kidney Foundation. *Am J Kidney Dis*. 2007;49(suppl 2):S1—S160.
5. IDF Global Guideline for Type 2 Diabetes 2012. Available at http://www.idf.org/guideline-type-2-diabetes. Accessed March 2017.
6. National Institute for Health and Care Excellence. Chronic Kidney Disease Guidelines.2015 **7.** Inzucchi SE et al. *Diabetes Care*. 2015;38:140–149. **8.** Deacon C et al. *Diabetes Obes Metab*. 2016;18:333–347.

Summary (continued)

- Sitagliptin has clinical evidence supporting use in patients with renal impairment [10]
- Nephrotoxicity is not noted as an adverse event in the literature and SPC. Dose reductions are required depending on the level of renal impairment. Doses in renal impairment are 100mg/day for GFR ≥45 to <90 mL/min; 50mg/day for GFR ≥30 to <45 mL/min ;25mg/day for GFR <30 mL/min. The dose reductions have demonstrated meaningful glucose-lowering efficacy and safety including patients with ESRD[1–3]
  - Did not increase the risk of CV events or eGFR decline in patients with established CV disease and renal impairment in the TECOS CV Safety Trial.[4]
    - Has not been associated with clinically meaningful eGFR reductions beyond the age-related decline seen in observational studies[5–9]
- Sitagliptin is the most widely prescribed DPP-4 inhibitor worldwide with a broad range of indications in patients with T2DM [11]

CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; T2DM = type 2 diabetes mellitus; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

1. Nauck MA et al. *Diabetes Obes Metab*. 2007;9:194–205. **2.** Arjona Ferreira JC et al. *Diabetes Care*. 2013;36:1067–1073. **3.** Arjona Ferreira JC et al. *Am J Kidney Dis*. 2013;61:579–587. **4.** Green JB et al. *N Engl J Med*. 2015;373:232–242. **5.** Cornel JH et al. *Diabetes Care*. 2016;39:2304–2310. **6.** Altemtam et al. *Nephrol Dial Transplant*. 2012;27:1847–1854. **7.** Ali O et al. *BMJ Open*. 2013;3:e001855. **8.** Premaratne E et al. *Diabetologia*. 2005;48:2486–2493. **9.** Rossing K et al. *Kidney Int*. 2004;66:1596–1605. **10.** Sitagliptin (Januvia) Summary of product characteristics.. 11. Data on file, DIAB-1237427-0000.

Cost of 12 months of Januvia and cost of dialysis; <£400 Vs £22,500

http://nww.lancashireteachinghospitals.nhs.uk/renal

Prescribing information

JANUVIA®
sitagliptin

PRESCRIBING INFORMATION
Refer to Summary of Product Characteristics (SmPC) before prescribing

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD (tel: 01992 467272), UK.

PRESENTATION
Film-coated tablets containing either 25 mg, 50 mg or 100 mg of sitagliptin

USES
For adult patients with type 2 diabetes mellitus Januvia is indicated to improve glycaemic control:
as monotherapy
- in patients inadequately controlled by diet and exercise alone and for whom metformin is contraindicated or not tolerated

as dual oral therapy in combination with
- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is contraindicated or not tolerated
- a PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control

as triple oral therapy in combination with
- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control
- a PPARγ agonist and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Januvia is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dosage of insulin do not provide adequate glycaemic control.

DOSAGE AND ADMINISTRATION
One 100 mg tablet once daily. When used in combination with metformin and/or a PPARγ agonist, maintain the dosage of metformin and/or PPARγ agonist, and administer sitagliptin concomitantly. When used in combination with a sulphonylurea or with insulin, consider a lower dose of sulphonylurea or insulin, to reduce risk of hypoglycaemia. Renal impairment: glomerular filtration rate [GFR] ≥45 to < 90ml/min): no dosage adjustment required; GFR ≥30 to <45 mL/min): 50 mg once daily; GFR <30 mL/min including those with endstage renal disease (ESRD) requiring haemodialysis or peritoneal dialysis: 25 mg once daily. Sitagliptin may be administered without regard to the timing of dialysis. Because of the above dosage adjustment, assessment of renal function is recommended prior to initiation of sitagliptin and periodically thereafter. When used with other anti-diabetic agent(s) in renal impairment, refer to SmPC(s) of the other agent(s). Hepatic impairment: mild to moderate hepatic impairment: no dosage adjustment necessary; severe hepatic impairment: no data available, exercise caution. Elderly: no dosage adjustment necessary. Children and adolescents <18 years: no data available.

CONTRAINDICATIONS
Hypersensitivity to active substance or excipients.

PRECAUTIONS
Do not use in patients with type 1 diabetes or for diabetic ketoacidosis. Use of DPP-4 inhibitors has been associated with a risk of acute pancreatitis and very rarely cases of necrotizing or haemorrhagic pancreatitis and/or death have been reported with sitagliptin. Inform patients of the symptoms of acute pancreatitis. If pancreatitis is suspected, sitagliptin and other potentially suspect medicinal products should be discontinued. If acute pancreatitis is confirmed, sitagliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis. On addition of sitagliptin to insulin or a sulphonylurea, consider a lower dose of insulin or sulphonylurea to reduce the risk of hypoglycaemia. Lower dosages are recommended in patients with GFR < 45 mL/min including ESRD patients requiring haemodialysis or peritoneal dialysis. Serious hypersensitivity reactions have been reported, including anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset occurred within the first 3 months after initiation of treatment with some reports occurring after the first dose. If suspected, discontinue sitagliptin, assess for other potential causes and initiate alternative treatment for diabetes. Cases of bullous pemphigoid have been reported. If suspected, discontinue sitagliptin.

Drug interactions:
Digoxin: monitor patients at risk of toxicity.

Pregnancy and Lactation:
Do not use during pregnancy or breastfeeding.

SIDE EFFECTS Refer to SmPC for complete information on side effects
Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycemia has been reported in combination with sulphonylurea and insulin. Sitagliptin monotherapy: *Common*: upper respiratory tract infection, nasopharyngitis, osteoarthritis, pain in extremity, hypoglycaemia, headache. Combination with metformin: *Common*: nausea, flatulence, vomiting. Combination with a sulphonylurea: *Common*: hypoglycaemia. Combination with metformin and a sulphonylurea: *Very common:* hypoglycaemia; *Common:* constipation. Combination with a PPARγ agonist (pioglitazone): *Common:* flatulence, peripheral oedema. Combination with a PPARγ agonist (pioglitazone) and metformin: *Common:* peripheral oedema. Combination with insulin with/ without metformin: *Common:* hypoglycaemia, influenza. *Serious adverse events with sitagliptin during post-approval use alone and/or with other diabetes medicines where frequency is not known:* hypersensitivity reactions including anaphylactic responses (see precautions), interstitial lung disease, acute pancreatitis, fatal and non-fatal haemorrhagic and necrotizing pancreatitis, angioedema, cutaneous vasculitis, exfoliative skin conditions including Stevens-Johnson syndrome, impaired renal function, acute renal failure.

PACKAGE QUANTITIES AND BASIC NHS COST
25 mg x 28 tablets: £33.26;
50 mg x 28 tablets: £33.26;
100 mg x 28 tablets: £33.26

Marketing Authorisation Number
25 mg: EU/1/07/383/002;
50 mg: EU/1/07/383/008;
100 mg: EU/1/07/383/014

Marketing Authorisation Holder
Merck Sharp & Dohme Limited,
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review of prescribing information:** December 2017

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