

NENC Guideline For Use Of Sodium Glucose Co-transporter 2 Inhibitors (SGLT2i) in Adults

Introduction & Scope

Aims of this document:

- To guide prescribing of SGLT2 inhibitors within each individual drug's current license
- To advise on appropriate choice of SGLT2 inhibitor
- To ensure safe and appropriate prescribing of SGLT2 inhibitors for patients
- To ensure that the necessary safety information is given to all patients

It is important to note this is only a guide and not exhaustive, appropriate clinical judgement and referral to other reference sources may be appropriate in individual patient cases. This resource is only for use in adults.

Licenses for SGLT2 inhibitors are changing rapidly. Always check the up-to-date licenses.

The information in this guidance was correct at the time of publication.

What are SGLT2 inhibitors?

- An established class of medications which are licensed for the treatment of:
 - Insufficiently controlled type 2 diabetes (T2DM)
 - Symptomatic chronic heart failure (HF) with reduced ejection fraction (with or without T2DM)
 - Chronic kidney disease (CKD) (with or without T2DM)
- SGLT2 inhibitors have been shown to reduce the risk of cardiovascular events in people living with T2DM and atherosclerotic cardiovascular disease (ASCVD) i.e., coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease
- They act by preventing the absorption of glucose and sodium, mainly from the proximal renal tubule in the kidney
- Glucose and sodium are, therefore, lost in urine
- People do not become hyponatraemic (unless co-prescribed diuretics) as most of the sodium is reabsorbed in the distal tubule
- This effect results in decreasing the blood glucose level, weight loss, an osmotic diuresis and a drop in blood pressure

Step 1: Identify if the person is suitable for an SGLT2 inhibitor – decide which SGLT2 inhibitor to use

Which SGLT2 inhibitor should I use?

Choice of SGLT2 inhibitor depends on co-morbidities.

One significant co-morbidity:

T2DM	HF	CKD*
Dapagliflozin or Empagliflozin	Dapagliflozin or Empagliflozin	Dapagliflozin

Two significant co-morbidities:

	T2DM	HF	CKD*	CKD**	ASCVD***
T2DM		Dapagliflozin or empagliflozin	Dapagliflozin	Dapagliflozin	Empagliflozin or dapagliflozin
HF	Dapagliflozin or empagliflozin		Dapagliflozin	Dapagliflozin	Empagliflozin or dapagliflozin
CKD*	Dapagliflozin	Dapagliflozin			Dapagliflozin
CKD**	Dapagliflozin	Dapagliflozin			
ASCVD***	Empagliflozin or dapagliflozin	Empagliflozin or dapagliflozin	Dapagliflozin		

Three or more significant co-morbidities (T2DM and/or ASCVD and/or HF and/or CKD*):

Dapagliflozin (or empagliflozin if no CKD)

We would not advocate switching between SGLT2 inhibitors if co-morbidity changes.

The above suggestions for initial therapy are based on licences and clinical trial data including cardiovascular outcome trials.

Criteria For Use:

T2DM	NICE guidance NG28 advises SGLT2 use in people with T2DM with established ASCVD or high risk of cardiovascular disease. NICE guidance NG28 advises SGLT2 use in people with QRISK2 of 10% or higher. NICE guidance states: Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease. https://www.nice.org.uk/guidance/ng28
HF	Patient symptomatic secondary to chronic heart failure with reduced ejection fraction NICE TA – Dapagliflozin for treating chronic heart failure with reduced ejection fraction: https://www.nice.org.uk/guidance/ta679 NICE TA – Empagliflozin for treating chronic heart failure with reduced ejection fraction: https://www.nice.org.uk/guidance/ta773
CKD*	* With albuminuria: urine ACR \geq 22.6mg/mmol and eGFR 25-75ml/min/1.73m ² either attributed to diabetic and non-diabetic causes in someone living with diabetes or in someone not living with diabetes excluding those with polycystic kidney disease or someone on immunological therapy for renal disease NICE TA – Dapagliflozin for treating CKD: https://www.nice.org.uk/guidance/ta775
CKD**	** with ACR < 22.6mg/mmol and eGFR 25-75ml/min/1.73m ²
ASCVD***	*** ASCVD is not a licenced indication and trial evidence for benefits in ASCVD in combination with other licenced indications have led to the choices in this guidance such as those stated in NG28 for T2DM as listed above.

Step 2: Check cautions and contraindications prior to prescribing

Who is likely to be at risk with SGLT2 inhibitors?

Use with CAUTION in the following situations:

- Patient Characteristics
 - Body mass index <25 kg/m² (<23 kg/m² in South Asian patients)
 - Person adhering to a ketogenic/low calorie/low carbohydrate diet
 - Recent weight loss
 - Potential for pregnancy
 - People at risk of hypotension/hypovolaemia (e.g. elderly)
 - People diagnosed with or at risk of frailty
 - Cognitive impairment or use of medication compliance aid (as this *may* imply inadequate understanding required to follow sick day rules and take action to prevent and identify DKA)
- Other Past Medical History
 - On long term or recurrent courses of steroids
 - Raised haematocrit
 - Severe hepatic impairment
 - Recurrent urinary or genital tract infections
 - Glomerulonephritis with flares (ANCA associated vasculitis or lupus nephritis) – consider discussion with nephrologist
 - Ongoing or recent requirements of cytotoxic, immunosuppressive or other immunomodulating renal therapy – consider discussion with nephrologist
- Diabetes History
 - Long duration of diabetes (generally over 10 years from diagnosis)
 - Person with very high level of HbA1c >86 mmol/mol
 - Person considered at high risk of acute effects of hyperglycaemia (e.g. dehydration due to non-adherence to medication)
 - Past history of active foot disease/foot ulceration
 - Existing diabetic foot ulcers, active foot disease
 - Previous lower limb amputation
 - History of peripheral arterial disease (PAD)
 - Taking sulphonylureas and/or insulin – increased risk of hypoglycaemia if commenced on SGLT2



CONTRAINDICATIONS –

AVOID in the following situations:

- Patient Characteristics
 - Age <18 years - this guideline is only for use in adults
 - Pregnant, breastfeeding, female in their child-bearing years and sexually active without contraception
 - Person with excess alcohol consumption or IVDU
- Current Medical History:
 - Acutely unwell person (acute medical illness including COVID-19, surgery or planned medical procedure)
 - Inpatient with acute vascular event who is not stable
 - Eating disorder
 - eGFR lower than allowed in the up-to-date licensing of the medication being considered
 - Organ transplant
 - Polycystic kidney disease
- Diabetes History:
 - Suspected or possible T1DM
 - Any diagnosis or suspicion of latent autoimmune diabetes (LADA), other genetic causes of diabetes, known pancreatic disease or injury, or people who rapidly progressed to needing insulin within 1 year of diagnosis
 - Past history of diabetic ketoacidosis



Step 3: Discuss with patient individualised benefits and risks around sick day rules

When initiating SGLT2 inhibitors: information for the patient

Before initiating SGLT2 inhibitors the patient should be advised:

- What the benefits of taking SGLT2 inhibitors are to them as an individual
- What side effects may occur and sick day rules (see below)
 - To seek urgent medical attention if symptoms of DKA
 - To seek urgent medical attention if symptoms of Fournier's gangrene (e.g. severe pain, tenderness, erythema, swelling in genital or perineal area)
- About the importance of routine preventative foot care
- To drink plenty of fluids to avoid dehydration unless they have been told to restrict fluids by a healthcare professional, for example due to heart or kidney problems

Reducing risk – patient education, sick day rules

All patients should be counselled on initiation of an SGLT2 inhibitor (by the initiating clinician) about sick day guidance and when to suspend taking their SGLT2 inhibitor due to associated risks with dehydration and development of DKA.

- If ill with diarrhoea, UTI, vomiting, fever or unusual drowsiness, SUSPEND SGLT2 inhibitors and don't restart until feeling better and eating/drinking fluids normally
 - Restart only AFTER eating normally for AT LEAST 24 HOURS AND no longer acutely unwell
- Encourage patient to avoid dehydration with appropriate fluid intake
 - Unless advised to restrict fluids, such as patients with HF. This may require discussion with HF specialist team to consider temporarily relaxing fluid restriction/increasing fluid intake
- ALL patients must be counselled on the risk of diabetic ketoacidosis (DKA) and its signs and symptoms (nausea, vomiting, abdominal pain, stupor, fatigue, difficulty breathing) and to STOP SGLT2 inhibitor immediately and seek urgent medical attention if any symptoms develop.
- To seek urgent medical attention if symptoms of Fournier's gangrene (e.g. severe pain, tenderness, erythema, swelling in genital or perineal area)
- Seek medical advice if particularly unwell with infection or illness
- Stop SGLT2 inhibitors prior to surgery—as advised by pre-op team

When initiating SGLT2 inhibitors: Prescribing considerations

- Minimise the risk of hypoglycaemia:
 - Review glucose lowering medications that may cause hypoglycaemia (e.g. insulin and sulphonylureas)
 - Consider dose reductions of glucose lowering medicines when SGLT2i initiated, particularly if HbA1c is already at target
- Minimise risk of Diabetic Ketoacidosis (DKA), check if the person may be at increased risk, for example if:
 - They have had a previous episode of DKA (contraindicated)
 - They are unwell with intercurrent illness
 - They are following a very low carbohydrate or ketogenic diet
- Minimise the risk of hypotension:
 - Review diuretic and anti-hypertensives if hypertension improves or if there is postural hypotension

Class Side Effects:

Common:

- Increased risk of UTI
- Polydipsia
- Polyuria
- Genito-urinary disorders
- Volume depletion effects (thirst, postural dizziness, hypotension, dehydration)
- Decreased eGFR
- Hypoglycaemia (increased risk if on sulphonylureas and/or insulin)

Uncommon but serious: (See MHRA alerts below for more information)

- DKA
- Lower limb amputation – encourage regular preventative footcare
- Fournier's Gangrene

Please see individual drug monograph in BNF/SPC for a complete side-effect profile – see hyperlinks in table above.

Step 4: Prescribe appropriate dose

- Note doses vary depending on indication renal, and hepatic function

SGLT2 Inhibitor	Indication	Dose Adjustments				Hepatic Impairment
		eGFR > 60ml/min/1.73m ²	eGFR 45-59ml/min/1.73m ²	eGFR 30-44ml/min/1.73m ²	eGFR <30ml/min/1.73m ²	
				<p>Note glycaemic benefit will be limited for all SGLT2i below eGFR of 45ml/min as the glucose lowering efficacy of SGLT2i therapy is dependent on renal function.</p> <p>At this level of eGFR, there may be only ASCVD and renal benefit. Further glycaemic control may be required.</p>		
Canagliflozin PIL/SPC	T2DM	<p>Initiate 100mg once daily, titrate to 300mg once daily if needed for glycaemic control</p> <p>Preferably taken before breakfast</p>	Initiate/continue with 100mg once daily only	<p>Not recommended for glycaemic control in T2DM in the absence of DKD due to lack of glycaemic efficacy.</p> <p>Initiate/continue with 100mg once daily.</p> <p>Further glycaemic control may be required.</p>	<p>Not recommended for glycaemic control in T2DM in the absence of DKD due to lack of glycaemic efficacy.</p> <p>Continue established treatment with 100mg once daily but do not initiate. Can continue until dialysis or transplant if ACR >30mg/mmol when eGFR falls below 30ml/min/1.73m². Stop if dialysis/transplant.</p> <p>Further glycaemic control may be required.</p>	No dose adjustment necessary if mild/moderate impairment.
	Treatment of diabetic kidney disease (DKD) in adults with type 2 diabetes (UKKA have advised to have uACR ≥25mg/mmol and/or eGFR 25-60 ml/min/1.73m ² for use in people living with diabetes)	<p>Initiate 100mg once daily, titrate to 300mg once daily if needed for glycaemic control</p> <p>Preferably taken before breakfast</p>	Initiate/continue with 100mg once daily only	Initiate/continue with 100mg once daily only	<p>Continue established treatment with 100mg once daily but do not initiate.</p> <p>Can continue until dialysis or transplant if ACR >30mg/mmol when eGFR falls below 30ml/min/1.73m².</p> <p>Stop if dialysis/transplant.</p>	Therapeutic experience in severe hepatic impairment is limited and therefore use is not recommended by manufacturer.
Dapagliflozin PIL/SPC	T2DM	<p>Initiate 10mg once daily</p> <p>Take with or without food</p>		<p>Not recommended for glycaemic control in T2DM.</p> <p>Do not initiate if eGFR <15ml/min/1.73m²</p> <p>Can continue with 10mg once daily if person also has symptomatic HFrEF or CKD down to eGFR of 15ml/min/1.73m²</p> <p>Further glycaemic control may be required.</p>		
	Symptomatic chronic HFrEF with or without diabetes	<p>Initiate 10mg once daily</p> <p>Take with or without food</p>			<p>Do not initiate if eGFR <15ml/min/1.73m²</p> <p>Can continue with 10mg once daily down to eGFR of 15ml/min.</p>	Initial dose 5mg daily in severe hepatic impairment, can increase to 10mg according to response/tolerability
	Chronic kidney disease (NICE have advised: for people with diabetes, you should have an eGFR 25-75ml/min/1.73m ² and : type 2 diabetes or a uACR ≥22.6mg/mmol)	<p>Initiate 10mg once daily</p> <p>Take with or without food</p>			<p>Do not initiate if eGFR <25ml/min/1.73m²</p> <p>Can continue with 10mg once daily down to eGFR of 15ml/min/1.73m², dialysis or transplantation.</p>	
Empagliflozin PIL/SPC	T2DM	<p>Initiate 10mg once daily, titrate to 25mg if required</p> <p>Take with or without food</p> <p><i>Initiation is not recommended in adults >85 years</i></p>	<p>Only initiate in those with established CVD, 10mg once daily</p> <p>For those already taking empagliflozin, continue with or reduce to 10mg once daily</p>	<p>Only initiate in those with established CVD, 10mg once daily</p> <p>Further glycaemic control may be required.</p>	<p>Not recommended for glycaemic control in T2DM</p> <p>Do not initiate and discontinue if eGFR <20ml/min/1.73m²</p> <p>Can continue with 10mg once daily if person also has symptomatic HFrEF down to eGFR of 20ml/min/1.73m². Further glycaemic control may be required.</p>	No dose adjustment necessary if mild/moderate impairment.
	Symptomatic chronic HFrEF with or without diabetes	<p>Initiate 10mg once daily</p> <p>Take with or without food</p>			<p>Initiate 10mg once daily if eGFR >20ml/min/1.73m²</p> <p>Do not initiate and discontinue if eGFR <20ml/min/1.73m²</p>	Therapeutic experience in severe hepatic impairment is limited and therefore use is not recommended by manufacturer.
Ertugliflozin PIL/SPC	T2DM	<p>Initiate 5mg once daily, titrate to 15mg once daily, if needed and tolerated</p> <p>Dose to be taken in the morning with or without food</p>	<p>Do not initiate.</p> <p>For those already taking ertugliflozin continue with 5mg once daily or 15mg once daily.</p>	<p>Do not initiate</p> <p>Discontinue if already taking</p>		

Step 5: Documentation, Monitoring and Ongoing Use

For all indications:

Documentation

The indication for SGLT2 inhibitor therapy must be clearly documented on the patient's medical record to ensure follow up and monitoring is appropriate. However it should be noted some patients may have multiple co-morbidities for which SGLT2 inhibitor therapy will confer benefit.

Monitoring: Additional monitoring after starting SGLT2 inhibitor is NOT required. It is worth noting that due to its mechanism of action, patients on SGLT2 inhibitor therapy will test positive for glucose in their urine

T2DM	People with T2DM <ul style="list-style-type: none">Patients with T2DM who are commenced on SGLT2 inhibitor therapy may require adjustment to their other glucose lowering medication and closer monitoring of HbA1c/capillary blood glucose following initiation of SGLT2i due to the potential for hypoglycaemia.<ul style="list-style-type: none">For patients with a HbA1c on initiation of SGLT2 therapy of <48mmol/mol or if HbA1c falls to <48mmol/mol during treatment with SGLT2 inhibitor, concurrent diabetes medication should be promptly reviewed to prevent risk of hypoglycaemiaThere is an increased risk of hypoglycaemia when SGLT2 inhibitor therapy is used alongside sulphonylureas and/or insulin
HF	Monitoring – Additional monitoring after starting SGLT2 inhibitors is NOT required. Routine monitoring of kidney function should continue as part of routine care, frequency guided by national and local guidance for T2DM, HF and/or CKD as appropriate, but additional routine tests are not required after starting SGLT2 inhibitor therapy. Increases in serum creatinine and urea are to be expected upon initiation of SGLT2 inhibitors, through changes to glomerular filtration pressure, and therefore do not necessarily indicate damage to the kidneys – local protocols regarding monitoring may differ.
CKD	Monitoring – Additional monitoring after starting SGLT2 inhibitors is NOT required. Routine monitoring of kidney function should continue as part of routine care, frequency guided by national and local guidance for T2DM, HF and/or CKD as appropriate, but additional routine tests are not required after starting SGLT2 inhibitor therapy. Increases in serum creatinine and urea are to be expected upon initiation of SGLT2 inhibitors, through changes to glomerular filtration pressure, and therefore do not necessarily indicate damage to the kidneys – local protocols regarding monitoring may differ.

Patient Information Leaflets and Useful Resources

For all indications, Patient Information Leaflets for each SGLT2 inhibitor can be accessed via: <https://www.medicines.org.uk/emc/>

T2DM	Useful resources for people living with diabetes: TREND leaflets (free to register): https://trenddiabetes.online/resources/ <ul style="list-style-type: none">Diabetes and your KidneysHow to reduce your risk of genital fungal infectionType 2 Diabetes and Diabetic KetoacidosisType 2 Diabetes: what to do when you are ill SADMAN Sick Day mnemonic: https://e7fvz575be6.exactdn.com/wp-content/uploads/pdf/dotn024ae8fb1b78500b7bc752b98e9b6d92.pdf ABCD SGLT2 inhibitor information: https://abcd.care/sites/abcd.care/files/site_uploads/images/ABCD_A4_Leaflet_Final%20%28002%29.jpg
HF	Useful resources for people living with heart failure: https://pumpingmarvellous.org/
CKD	Useful resources for people living with kidney disease: https://guidelines.ukkidney.org/

Contacts and Communication

T2DM	Please use usual referral/advice and guidance processes for further advice
HF	<ul style="list-style-type: none">County Durham and Darlington NHS Foundation Trust: Professor Murphy, HF lead, jerry.murphy@nhs.netGateshead Health NHS Foundation Trust: Hamza Khalil, Advanced Specialist Pharmacist, Heart Failure, hamza.khalil1@nhs.net, Claire Davies, Diabetes and Endocrinology Specialist Pharmacist, claire.davies62@nhs.netNewcastle upon Tyne NHS Foundation Trust: Dr Kristian Bailey, Consultant Cardiologist, kristian.bailey2@nhs.netNorthumbria Healthcare NHS Foundation Trust: Alastair Green, Senior Clinical Pharmacist - Cardiology, Alastair.green@northumbria-healthcare.nhs.ukNorth Cumbria Integrated Care NHS Foundation Trust, West Cumberland Hospital (WCH) Heart Failure Team: 07824 351769, Cumberland Infirmary Heart Failure Team: 07824 383884South Tyneside and Sunderland NHS Foundation Trust: stsft.sunderlandheartfailureteam@nhs.netSouth Tees Hospitals NHS Foundation Trust: Dr Jeet Thamyrajah, Consultant Cardiologist, jeet.thamyrajah@nhs.netFor other Trusts please use usual referral/advice and guidance processes for further advice.
CKD	<ul style="list-style-type: none">For areas served by South Tees Renal Service, advice can be sought via: stees.renal@nhs.netFor areas served by Newcastle upon Tyne Renal Service, advice can be sought via electronic referral, 'Advice and Guidance' to NephrologyFor areas served by Sunderland Renal Service, advice can be sought via electronic referral, 'Advice and Guidance' to NephrologyFor areas served by North Cumbria Integrated Care/Renal Service, advice can be sought via usual referral process

Further Information

Additional Important safety information – Please see hyperlinks for more detailed advice:

- [MHRA/CHM advice \(updated April 2016\): SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis \(DKA\)](#)
 - People should be informed on the signs and symptoms of DKA, discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed
 - Test for raised ketones in patients with ketoacidosis symptoms, even if plasma glucose levels are near-normal
- [MHRA/CHM advice \(MHRA/CHM advice March 2017\): SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation \(mainly toes\)](#)
 - SGLT2i's may increase the risk of lower-limb amputation (mainly toes). All people taking an SGLT2i inhibitors should be counselled on good preventative foot care. Review if lower limb complications develop (e.g. skin ulcer, osteomyelitis, or gangrene). Monitor people with risk factors for amputation.
- [MHRA/CHM advice: SGLT2 inhibitors: reports of Fournier's gangrene \(necrotising fasciitis of the genitalia or perineum\) \(February 2019\)](#)
 - If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement as required)
 - Fournier's gangrene is a rare but potentially life-threatening infection that requires urgent medical attention
- [MHRA/CHM advice: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness \(March 2020\)](#)
 - SGLT2 inhibitor treatment should be interrupted in people who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine. Treatment may be restarted when the ketone values are normal and the person's condition has stabilised
- [MHRA/CHM advice: Dapagliflozin \(Forxiga\): no longer authorised for treatment of type 1 diabetes mellitus](#)
 - The authorisation holder for dapagliflozin has withdrawn the indication for type 1 diabetes mellitus. The removal of the type 1 diabetes indication is not due to any new safety concerns and the other indications of dapagliflozin are unchanged

SGLT2 Inhibitors – Lower Limb Amputation Risk. Northern Diabetes Foot Care Network Statement

The Northern Diabetes Foot Care Network initially reviewed the available literature on the risk of lower limb amputation (major & minor) associated with the class of oral glucose-lowering drugs known as Sodium Glucose Co-transporter type 2 (SGLT2) inhibitors and issued a position statement in September 2017. This is an update.

We highlight, that within the CANVAS trial programme, the SGLT2 inhibitor canagliflozin significantly reduced the risk of cardiovascular events by 14% but doubled the risk of lower limb amputation in patients with Type 2 diabetes¹. [http://www.thelancet.com/pdfs/journals/landia/PIIS2213-8587\(17\)30257-7.pdf](http://www.thelancet.com/pdfs/journals/landia/PIIS2213-8587(17)30257-7.pdf)

Two Systematic reviews/Meta-Analyses have been published in 2020, both of which fail to identify an increase in lower limb amputation risk with SGLT2 inhibitors:

https://www.onlinejacc.org/content/75/11_Supplement_1/2281

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0234065>

With this evidence in mind we have issued the following recommendations.

1: CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; published online June 12. DOI:10.1056/NEJMoa1611925.

Recommendations

- 1: All patients with diabetes should undergo annual foot checks, their risk identified as Low, Increased, High or Active disease/Ulcer, and patients must be made aware of their individual risk category.
- 2: All patients with diabetes should be made aware of their potential risk and advised to seek urgent medical advice if they develop a diabetic foot ulcer.
- 3: SGLT2 inhibitors as a class do not show a significant increased risk of lower limb major amputation and should be continued in people with high risk and actively ulcerated feet, provided that clinical benefit has been adequately demonstrated with a reduction in HbA1c.
- 4: It should be noted that there is heterogeneity in the systematic reviews and that the CANVAS study continues to show an increased risk of amputation with canagliflozin. The risks of benefits of this agent compared to other SGLT2 inhibitors should be considered in all people with diabetes and consideration given to switching to an alternative SGLT2 inhibitor.
- 5: Given the link between Euglycaemic Ketosis and ALL SGLT2 inhibitors. These agents must be stopped prior to any surgical intervention.