Airedale, Wharfedale and Craven
Bradford Districts
Bradford City
CCGs working together
NHS

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Bradford and Airedale
Prescribing Guidelines for the Diabetes Management

Aim

The aim of this guidance is not to restrict choice but to ensure that the most clinically appropriate and effective treatment is prescribe to achieved the individualised HbA1c target agreed with the person with Diabetes. To achieve this it is essential that the impact of all treatments initiated are evaluated to ensure a positive impact on glycaemic control has been achieved. If an adequate positive response has not been noted the treatment options should be reviewed.

General messages

1. Where a choice between similar products exists, it is expected that patients will start on the cheapest products unless compelling clinical reason to the contrary
2. Starting criterion need to be adhered to strictly
3. Stopping criterion are equally if not more important.
4. If it is clear a patient has **not** responded to a medication and another medicine is to be tried the first medicine should be stopped.
5. Check compliance and concordance with medicine use. Is the patient taking the medicines that you have prescribed for them in the right way?
6. Injectable therapy should **not** be initiated outside level 2 or 3 care.
7. Response should be reviewed regularly and adjustments made to dose, checking compliance.
8. Patients currently on gliptins, SGLT2 inhibitors and pioglitazone should be accessed to ensure that the introduction of these treatments had a positive impact on control in line with NICE guidance when introduced otherwise should be discontinued if a drop of mmol/mol in 6 months was not noted.
9. **No** Blanket switches should be implemented all treatment changes should be discussed with the person with diabetes before implemented.

Content

Section 1

First line therapy

The management of type 2 diabetes usually begins with lifestyle modifications then oral hypoglycaemic drugs.
The importance of lifestyle support must be emphasised throughout in all discussions with patients about glycaemic control. Modest increases in exercise, changes in diet and modest weight loss can achieve significant improvements in glycaemic control

Metformin is recommended as the **first-line** oral hypoglycaemic agent in most patients with type 2 diabetes when glycaemic control cannot be achieved by lifestyle interventions alone.
Estimated that 60-70% of patients initiate pharmacotherapy on metformin

Preparation	Recommendations	Rationale	Notes
Metformin Standard Format To a **maximum** dose of 2 grams <u>Poor to no evidence of glycaemic benefit > 1700mg</u> Titrate the dose slowly – initially 500mg after evening for at least one week, then add 500mg with breakfast for one week, then add lunchtime dose if necessary.	In patients with a BMI greater than 25 or 23 if South Asian	Ideal first line treatment in type 2 diabetes especially in people who's BMI 25 and above when glycaemic control not achieved through lifestyle change alone.	**Metformin MR ONLY** to be used if intolerant of standard metformin or concordance issue Maximum dose 2g OD, post evening meal. **Metformin Oral solution** should **NOT** be used unless in exceptional circumstances annual cost £1440. Any patients currently using Metformin Granules should be reveiwed.as they have been withdrawn. Standard release Metformin can be crushed.

Alternative

Preparation	Recommendation	Rationale	Notes
Glimepiride 1mg to 4mg	1st line choice for those with a BMI <25 or<23 if South Asian. Symptomatic patients	• Tablet load • Cost • Licensed in combination with insulin • Tablets halve easily so simple to reduce dose if hypoglycaemia becomes an issue. • Can be used in patients with eGFR >10	**Glimepiride 1- 4mg** this product has a dosing and compliance advantage and is therefore recommended as the sulfonylurea of choice **Gliclazide 40mg OD in elderly patients in whom low dose treatment indicated** There is a slightly reduced hypoglycaemia risk than glimeperide though this advantage is very small in absolute terms and not statistically significant but in patients where a low start dose is indicated e.g. the elderly the 40 mg dose may be indicated. **Gliclazide MR** is **not** recommended based on cost and tablet load

Second line therapy

Preparation	Recommendation	Rationale
First line therapy not used		NICE recommendations 2009

	Glimepiride	Metformin	Pioglitazone .	DPP-4 inhibitor	SGLT2 Inhibitor	Insulin (basal)
Efficacy **Hypo risk** **Weight** **SE** **Co**st	High Moderate risk Gain Hypoglycaemia Low	High Low Loss GI side effects Low	High Low risk Gain Oedema,Heart failure, fractures Low	Intermediate Low risk Neutral Rare (pancreatitis reported) High		Highest High risk Gain Hypoglycaemia Variable

The Bottom Line

Sulfonylureas are the most cost-effective second-line therapy in patients with diabetes inadequately controlled on metformin, primarily because of their lower cost compared with insulin and newer drugs.

A number of options are available for use as second-line therapy when metformin is inadequately effective. Current guidelines vary when recommending a second-line treatment, and usually little to no evidence is cited in relation to these recommendations.

Sulfonylurea Added to Metformin — Quick Facts:

A1C lowering efficacy: ↓ by 0.8%.*
Change in weight: ↑ by 2 kg.*
Annual risk of hypoglycaemia requiring third-party assistance: 1 in 175 patients. (Home et al 2007)
Added cost per day: 5.7p

General notes

- All second line drugs achieved statistically significant reductions in A1C, ranging from 0.6% to 1.0%, and there were no statistically significant differences between drug classes.
- Events of severe hypoglycaemia were very rare for all drugs; however, the insulin's, sulfonylureas, and meglitinides were associated with a higher risk for overall hypoglycaemia than the other drugs.
- Compared with metformin alone, sulfonylureas, meglitinides, pioglitazone, and insulins were all associated with a modest increase in body weight (1.8 kg to 3 kg); dipeptidyl peptidase-4 (DPP-4) inhibitors and alpha-glucosidase inhibitors were weight-neutral, while glucagon-like peptide-1 (GLP-1) analogues were associated with weight loss (about 1.8 kg).
- There is insufficient evidence regarding the effect of second-line oral hypoglycaemic agents on the long-term complications of diabetes or mortality.
- In contrast to the other drugs, however, it should be noted that long-term safety data are available for sulfonylureas and human insulins as a result of their use in the landmark United Kingdom Prospective Diabetes Study.2
- Self blood glucose monitoring should be discussed in line with DVLA guidance for patients commenced on insulin and sulfonylurea therapy

Alternative second line therapy options

Preparation	Recommendation	Rationale	Notes
Insulin	Insulin is to be used with: • Patients symptomatic of hyperglycaemia who are not overweight, suggesting beta cell failure over insulin resistance • Where there is a concern that the patient diagnosis is late onset type 1 rather than type 2 diabetes • Where a rapid improvement in glycaemic control is needed e.g. surgery, chemotherapy • Pre conceptual care – with referral to secondary care diabetes unit • Swallowing difficulties • All other 2nd line therapy is contraindicated or not tolerated	NICE 2009	**Refer to L2.** Do NOT start this therapy in L1
Pioglitazone	To considered second line if SU or Metformin is contraindicated or not tolerated As an addition to Metformin where personal issues make the risk of hypoglycaemia with an SU significant. To be managed on lowest effective dose	NICE 2009	Pioglitazone increases the risk of oedema, heart failure, and fractures and link to bladder Ca. It is contraindicated in patient with CCF, Osteoporosis or Oesteomalcia history or risk factors for bladder cancer or undiagnosed haematuria, Should be stopped if reduction of HbA1c of **6 mmol /mol** not achieved after 6 months
Gliptin	**Second line** with **Metformin** instead of a sulfonylurea when HbA1c >48mmol/mol or above agreed target if: • Patient at significant risk of hypoglycaemia or its consequences, older people and people in certain jobs e.g. working at heights, heavy machinery people in certain social circumstances e.g. those living alone or • The person does not tolerate a sulfonylurea or it is contraindicated	NICE 2009	Should be stopped if reduction of HbA1c **6mmol / mol** is not achieved after 6months Maybe suitable alternative for occupational drivers as no indication for SBGM Identify suitable Gliptin based on

	Second line with a **Sulfonylurea** monotherapy when HbA1c >48mmol/mol or above agreed target if: • Metformin not tolerated or is Contraindicated		patient **eGFR and prescribing restrictions.** **See Which Gliptin and relevant section of the BNF**
SGLT2 inhibitor	**Second line** with **Metformin** instead of a sulfonylurea when HbA1c >48mmol/mol or above agreed target if: • Patient at significant risk of hypoglycaemia or its consequences, older people and people in certain jobs e.g. working at heights, heavy machinery people in certain social circumstances e.g. those living alone or • The person does not tolerate a sulfonylurea or it is contraindicated • Weight is an issue **Second line** with a **Sulfonylurea** monotherapy when HbA1c >48mmol/mol or above agreed target if: • Metformin not tolerated or is Contraindicated Weight is an issue	NICE 2014	Should be stopped if reduction of HbA1c **6mmol / mol** is not achieved after 6months Maybe suitable alternative for occupational drivers as no indication for SBGM **Must not be prescribed in patients with eGFR<60** **Use with Caution in over 75's and those at risk of volume depletion**
GLP-1	Currently GLP-1 medication **is not advised** as second line therapy. **However**, if a patient has tried other therapies and are unable to tolerate or are contraindicated then a GLP-1 may be used in a combination in dual therapy.		**Refer to level 2**

Third Line therapy

General messages

- **Human Insulin is probably the most cost effective option for a third line therapy. It is associated with *HbA1C lowering efficacy:*** ↓ by 1.2%.
- **If no response to second line treatment**, the efficacy of the 2nd line treatment should be assessed and be stopped prior to adding in third line
- If a decision is taken to commence patient on oral triple therapy at 3rd line, as opposed to commencing insulin treatment, the prescriber should very clearly give a timeframe of 6 months to achieve therapeutically useful gains in glycaemic control or insulin must be commenced
- There is no clear difference between different drug classes when adding a third agent to treat patients already prescribed metformin and sulfonlyurea (Gross et al 2011).
- Third line oral medicines achieve statistically significant, but modest (in absolute terms) reductions in HBA1C (compared to that achieved though insulin therapy). Insulin is considered the most effective third line agent in a meta analysis.
- Events of **severe** hypoglycaemia in T2 Diabetes are very rare.
- For insulin *annual risk of hypoglycaemia requiring third-party assistance is* 1 in 85 patients (based on Holman et al 2004 and Singh et al 09).
- Weight gain of 1.8-3kg is associated with insulin, DPP4 inhibitors are weight neutral, GLP1 analogues are associated with weight loss of 1.8 kg.
- The choice of third line agent should be based on cost, patient characteristics (including the clinical importance of weight gain and the incidence of hypoglycaemia) and patient preferences with in the confines of NICE guidance

Specific recommendations for third line

Preparation	Recommendation	Notes
Insulin	Insulin should be considered as first option for 3rd line treatment unless: • Patients declines insulin therapy at this point • Patient is overweight and further weight gain is an issue	**Refer to level 2** Human Insulin is probably the most cost effective option for a third line therapy. It is associated with *HBA1C lowering efficacy:* ↓ by 1.2%. **See which insulin**
Glimepiride	If not used as second line therapy due to concerns with hypoglycaemia	
Pioglitazone	Pioglitazone is to be used as 3rd line in the following situations: • In combination with Metformin and SU where insulin is likely to be unacceptable because of employment, social recreation issues related to potential hypoglycaemia, injection anxiety or personal preference • Obesity/metabolic syndrome • Evidence of insulin resistance rather than beta cell failure	Pioglitazone increases the risk of oedema, heart failure, and fractures and link to bladder Ca. It is contraindicated in patient with CCF, Osteoporosis or Oesteomalcia history or risk factors for bladder cancer or undiagnosed haematuria, Should be stopped if reduction of HbA1C of **6 mmol /mol** not achieved after 6 months
Gliptin	Patient refusing Injectable therapy and Glitazone or Metformin contraindicated or not tolerated	Should be stopped if reduction of HbA1c **6mmol / mol** is not achieved after 6months Maybe suitable alternative for occupational drivers as no indication for SBGM Identify suitable Gliptin based on patient **eGFR and prescribing restrictions.** **See Which Gliptin and relevant section of the BNF**
Canagliflozin/ Empagliflozin **(Dapagliflozin not recommend by NICE for triple therapy or licensed with Pioglitazone)**	Patient refusing Injectable therapy and Glitazone or Metformin contraindicated or not tolerated • Weight an issue	Should be stopped if reduction of HbA1c **6mmol / mol** is not achieved after 6months **Must not be prescribed in patients with eGFR<60 to be stopped if eGFR<45** **Use with Caution in over 75's and those at risk of volume depletion** **Not to be used in combination with Gliptin**

Which insulin

Preparation	Recommendation	Rationale
Human Insulin • **Humulin I** • **Humulin M3** • **Insuman comb 25** • **Insuman comb 50** • **Insuman Comb 15**	Human insulin should be used in the first instance NICE 2009	Range of pen devices Only human 50:50 mixture
Basal Analogue **Lantus**	If Third party involved in giving injections Nocturnal hypoglycaemia Type 1 diabetes	Cost cheaper than Levemir Can be injected at anytime in the day
Analogue Mixtures **Humalog Mix 25 or 50**	To use an analogue insulin if the following apply: • If patient/carer prefers to inject immediately pre meals • If hypoglycaemia is a problem • Marked post prandial excursion	Choice of pen devices and option to switch if indicated to 50/50 mixture
Rapid acting Analogue Insulin **Humalog** **Novorapid** **Apidra**	Type 1 diabetes Patient preference for pen device	NICE (2011)

Which GLP 1

Preparation	Recommendation	Rationale
Lixenatide	If GLP 1 Indicated	Cost and once daily
Dulaglutide	If compliance with bd injections an issue	Device and injection frequency

- Start with Lixenatide
- If respond well to Lixenatide consider moving to Exenatide once weekly (Bydureon)
- If cannot tolerate Lixenatide from nausea / other side effects, but responding to GLP 1, consider moving to Liraglutide

Which Gliptin- N.B. **If Gliptin indicated dose based on eGFR**

Preparation	Recommendation	Rationale	Evidence
Alogliptin 25mg	**eGFR >50**	Cost	BNF October 2014
Linagliptin 5mg	**If eGFR < 50** as **dual** therapy with Metformin or triple therapy with Metformin and Glimepiride	**No** renal restriction	BNF October 2014

Appendix 1
Blood glucose monitoring

District wide guidance is agreed

- If on a sulfonylurea self blood glucose monitoring the patient should be discussed with the patient especially if a driver. Class 2 drivers must test x 2 daily to enable renewal of their license.
- If on diet ± metformin – patient should not be routinely self testing **But** if completed Xpert and expresses a desire to monitor should be agreed in line with local guidance. Strips would **not** be add to repeat prescription but issued at diabetes review.
- If patient prescribed insulin – strips should be prescribed on repeat prescription in line with requirements based on frequency of test pattern agreed.
- If patient prescribed sulfonylurea strips should be prescribed on repeat a minimum of a box every 3 months.
- Meters issued should be in line with current district wide recommended meter list

Guidelines on Self Monitoring of Blood Glucose (SMBG) in Patients with Diabetes (Summary Sheet)

Key Practice points

- Patients who self monitor **must be** given adequate training in self –monitoring techniques.
- Self- blood glucose monitoring should form part of a wider programme of management.
- Patients and health care professionals should be clear about what they hope to achieve by self-monitoring of blood glucose.
- Pharmacists **should not** sell blood glucose monitoring equipment to patients without prior discussion with the patients diabetes care team
- Frequency of SBGM should be reviewed regularly and excessive use addressed.

Diabetes Type	**Treatment Group**	**Monitoring Regime**	**Reasonable Blood Glucose Strip requirements**	
Type 1 Diabetes	All people with Type 1 diabetes	SMBG is an integral part of treating Type 1 diabetes Patients should be educated to SMBG and adjust treatment accordingly The majority of patients with Type 1 diabetes should be able to monitor 4 or more times a day to prevent hypoglycaemia and control hyperglycaemia	**Initiation** 3 boxes	**Repeat prescription requirements** 5 boxes every 2 months
Intensive management or loss of hypoglycaemic awareness	Frequent testing essential in patients using pump therapy or carbohydrate counting	**A management plan should be developed and agreed with the individual** up to 8 tests daily	5 boxes every month	5 boxes every month
Pregnancy	All pregnant women with pre-gestational and gestational diabetes	All should SMBG at least 4 times a day to include both fasting and post prandial blood glucose measurements.	3 boxes monthly	5 boxes every 2 months
Type 2 Diabetes	Insulin therapy +/- hypoglycaemic agents	Consider SMBG 2 to 4 times a day. This may be reduced to once daily if glycaemic control is considered to be stable Increase testing during periods of illness or instability Assess patients understanding and use of results to adjust lifestyle and treatment. Provide extra training if required	2 boxes	1 box every 1 to 2 months
	Sulphonylurea alone or in conjunction with other therapies	Patients should monitor to identify the effects of treatment and to reveal or refute hypoglycaemia which may be asymptomatic- **Class 2 drivers** will need to be testing x2 daily Pattern of monitoring should be agreed as part of a management plan – with all drivers in line with DVLA guidance	1 box to facilitate monitoring agreed	1box every 3 months on repeat
	Diet & Physical Activity alone +/- metformin or glitazones or exenatide	**SMBG not routinely recommended as part of routine care** Glycaemic control is best monitored through HbA_{1c} testing motivated patients may wish to monitor effects of changes in diet and physical activity Urine glucose testing can be a useful guide for day to day control	Issued as required with agreement and education of the patient	No repeat prescription, Issue on request

Appendix 2
Prescribing for Erectile Dysfunction (ED) in men with diabetes

PDE-5 Medications

The PDE-5 medications Sildenafil 100mg, is the first line treatment for the management of ED in men with Diabetes unless contra indicated or not tolerated.an initial prescription of (8-12 tablets should be issued with advice to take PRN

Tadalafil and Vardenafil are alternative treatment for men with diabetes who require treatment for erectile dysfunction. Vardenafil and Sildenafil have a short lasting action and can be described as medication to use as required. Tadalafil has a longer action profile and can be used for patients who may require the medications effects to last for a longer time action.Guidelines for men with diabetes suggest initiating the drug of choice at the highest dose (unless the patient has moderate to severe renal disease). A trial of therapy of at least 8 doses is required to assess effectiveness (BSSM 2007).

Medication	Cost
Sildenafil 4x100mgs Tablets	£ 2.23
Tadalafil 4x20mgs	£26.99
Vardenafil 4x20mgs	£23.48

Schedule 11 (1998) suggests drugs for ED can be prescribed as 4 treatments or tablets per month however schedule 11 also suggests increased treatments can be prescribed at the discretion of the prescriber. In some circumstances tadalafil can be prescribed as a twice weekly preparation as this is a longer acting preparation lasting for up to 72 hours and is therefore useful for patients requiring spontaneity or for men with diabetes who do not respond to a an 'as required approach'.
A once daily tadalafil is also available as a 5mgs tablet –this is sometimes considered for patients in whom twice weekly tadalafil is effective or for whom other preparations/dosage give side effcts. This is prescribable for patients with diabetes under NHS schedule 11 prescribing.

Cost comparison

Tadalafil 8x20mgs	£53.98
Tadalafil 5mgs Once daily	£54.99

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A recent dispersable Vardenafil medication has been produced at a dose of 10mgs only . This is **not** currently being prescribed within BEDSS clinic.
For Patients who do not respond to one PDE-5 medication another one is trialled. The side effect profile for all 3 drugs is similar but different drugs can produce a different range of side effects. In addition if one PDE-5 does not work a second drug may have a better response.

For patients for who PDE-5 medications is not effective, Contra-indicated or who have side effects then alternative treatments such as vacuum therapy devices or intra –urethral aprostadil or as intra penile injections is available.

Vacuum devices.

These devices are prescribable under schedule 11 NHS prescribing for ED. The cost for these devices varies from £160 to £ 190 depending on the manufacturer. However they can be described as cost effective treatments as apart from initial prescribing costs further NHS prescribing is for replacement constriction rings only. The devices used in BEDDS clinic tend to be the Imedicare System who provide a healthcare trainer to teach patients how to use the device or the Osborne Esteem system which has a aftercare service including access to helpline, healthcare trainer plus an initial DVD demonstrating how to use .

Alprostadil Injections.

This is often used as second line treatment for Patients who do not respond to PDE-5s or in whom these drugs are contra indicated. (dependent on patient preference) Caverject Dual chamber is demonstrated at drug of choice due to the easier application, the Viridal Duo preparation is used for patients who require doses higher than 20mgs as Caverject dual chamber is not available in doses above 20mgs.

Intra cavernosal injection of Alprostadil

Caverject Dual Chamber 2.5-10mcgs = £7.35
Caverject Dual chamber 5-20mcgs = £9.50

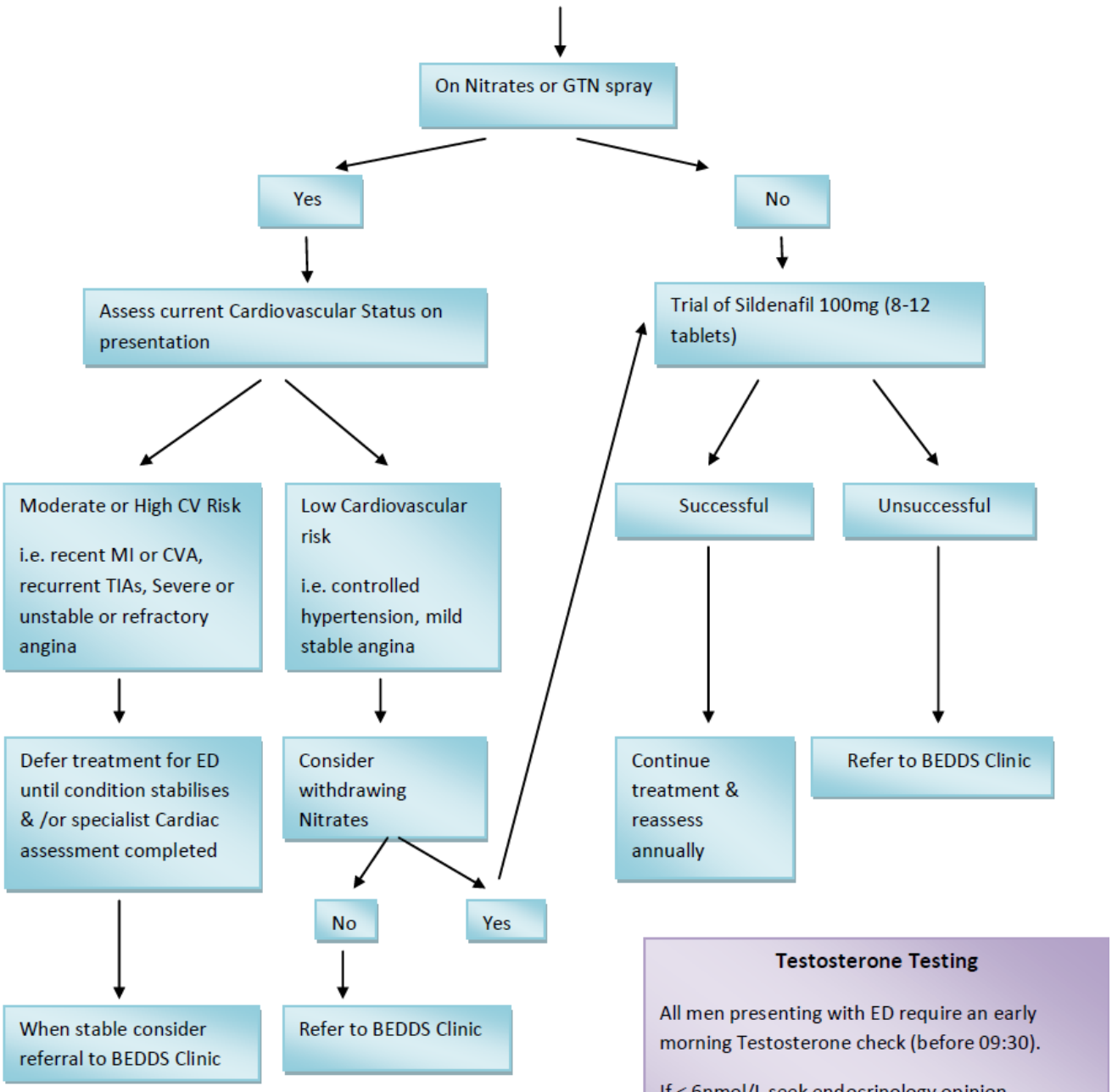
Viridal duo 10 microgram £20.13
20 microgram £24.54
40 microgram £29.83
(BNF 2012)

Alprostadil Intra urethral Pellets

As injection therapy above often used as a second line treatment especially for patients who decline injection therapy or for whom Vacuum therapy is not suitable.
Doses available from 250microgram to 1mg Dose, Cost from £11.30 to £11.56
(BNF 2012)

Repeat Prescribing
GPs are tasked via systmone or via a letter for non systemone practices of all prescribing decisions as per trust guidance for non medical prescribers.

Bradford Erectile Dysfunction Diabetes Service Referral pathway



PDE5 inhibitors

- contraindicated with Nitrates &/or GTN spray

- use with caution with Alpha-blockers as antihypertensive therapy

Testosterone Testing

All men presenting with ED require an early morning Testosterone check (before 09:30).

If < 6nmol/L seek endocrinology opinion.

If borderline between 6-12nmol/L & PDE5 inhibitor failure refer to BEDDS.

If referring to BEDDS this is automatically done following assessment.

NICE (2008) Type 2 diabetes; the management of type 2 diabetes (update). London: NICE
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NICE (2014) Canagliflozin in combination therapy for treating of Type 2 diabetes https://www.nice.org.uk/guidance/ta315/resources/guidance-canagliflozin-in-combination-therapy-for-treating-type2-diabetes-pdf accessed 29.10.14

Schedule 11 Prescribing reccomndations For Prescribing Drugs for Erectile Dsyfunction .NHS 1998

Sildenafil Summary of product Characteristics Pfizer Limited 2010

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Stoke on Trent NHS (2011) Options for patients unable to take solid oral dosage forms http://www.medicinesmanagementstoke.nhs.uk/documents/Crushing_Tabs_FAQs_December_2011_FINAL.PDF accessed 29.10.14

Tadalafil Summary of product Characteristics Eli Lilley and Company 2010

Vardenafil Summary of product Characteristics Bayer Healthcare 2010