Prescribing of Hypoglycaemic Agents for Adult Patients with Type 2 Diabetes: Sunderland

SU	Sulphonylurea
TZD	Thiazolidinedione (Glitazone)
DPP4i	Dipeptylpeptidase 4 inhibitor (Gliptin)
GLP- 1RA	Glucagon-Like-Peptide 1 Receptor Agonist
SGLT2i	Sodium Glucose Co-Transporter 2 Inhibitor

Refer to DESMOND – Structured Education classes to promote Increased Physical Activity, Weight Loss and Calories Reduction

if significant osmotic symptoms present at diagnosis and/or Excessive weight loss – re-consider diagnosis ? Type 1 – if rapid therapeutic response is required consider INSULIN & Monitor Carefully

HbA1c above Target (48 mmol/mol) despite Diet, Exercise and Lifestyle

STEP 1 – Start – **METFORMIN – 1st Line –** if intolerant give METFORMIN SR with or after food

→ IF CONTRAINDICATED → Commence SU

Arrange 3 Monthly Review – Re-enforce LIFESTYLE advice and check DRUG COMPLIANCE at each visit

STEP 2: Add one of:

HbA1c above Target (48mmol/mol) despite re-enforcement of Diet, Exercise and Lifestyle Modification – ALL glucose lowering therapies MUST be individualised to suit your patient

If a chosen option is ineffective in step 2, stop this & consider an alternative option before moving onto step 3

Class of Agent – Step 2	SU		TZD	DPP4i	SGLT2i
Preferred Choice/Option	TRADITIONAL PATHWAY	or if S/E or C/I	Alternative Pathway: OPTION 1	OPTION 2	OPTION 3
Expected HbA1c Reduction	11 – 16.5 mmol/mol (1 – 1.5%)		11 – 16.5 mmol/mol (1 – 1.5%)	5.5 – 10 mmol/mol (0.5 – 0.9%)	6 – 13 mmol/mol (0.5 – 1%)
Risk of Hypoglycaemia	HIGH		LOW	LOW	LOW
Weight Change	2kg GAIN		6kg GAIN	NEUTRAL	3kg LOSS
Key Side Effects	HYPOGLYCAEMIA		HEART FAILURE, OEDEMA, **	GI UPSET/PANCREATITIS	GENITAL INFECTION/UTI **
Cost	LOW – £30/yr		LOW - £20/yr	HIGH £430/yr	HIGH £475/yr
Target HbA1c Reduction	titrate dose to target glucose		6 mmol/mol after 6months	6 mmol/mol after 6months	6 mmol/mol after 6months

Arrange 3 Monthly Review – Re-enforce LIFESTYLE advice and check DRUG COMPLIANCE – Target HbA1c < 53mmol/mol

STEP 3: Add or Substitute with one of

HbA1c above Target (58mmol/mol) despite re-enforcement of Diet, Exercise and Lifestyle Modification –
- **ALL glucose lowering therapies MUST be individualised to suit your patient –**
- **STOP ANY AGENT THAT FAILS TO ACHIEVE TARGET HBA1c REDUCTION – esp the newer more expensive agents**

Class of Agent – Step 3	HUMAN BASAL INSULIN	GLP-1RA (DO NOT use with DPP4i or SGLT2i)	Combination Oral Therapy with MF (if insulin not accepted or appropriate). MF + SU + TZD & EITHER DPP4i OR SGLT2 ONLY
Preferred Injectable Choice & Option	TRADITIONAL PATHWAY – Continue MF & SU other oral agents ONLY continued if evidence of HbA1c reduction	OPTION 4: if BMI > 35kg/m2 or if BMI < 35kg/m2 if further weight gain or insulin unacceptable	+ SU
Expected HbA1c Reduction	Greater than 11 mmol/mol (1%)	11 – 16.5 mmol/mol (1 – 1.5%) over 6 moths	+ TZD
Risk of Hypoglycaemia	HIGH	LOW	Either + DPP4i
Weight Change	4kg GAIN – re-enforce DIET & LIFESTYLE to prevent this	4 - 6kg LOSS	OR + SGLT2i ** see overleaf
Key Side Effects	HYPOGLYCAEMIA	GI UPSET	
Cost	Variable - £160/yr	HIGH – £650 - 1400/yr	
Target HbA1c Reduction	11 mmol/mol after 6months	11 mmol/mol & 3% Weight loss after 6months	

Remember: T2DM is a progressive condition and re-enforcement of lifestyle advice & assessment of concordance with medication at each visit is vital.
DO NOT prescribe any agent in women of reproductive age without first assessing safety, preconceptual care and contraception.

Notes on Prescribing Glucose Lowering Medication

1: Diagnosis should be based on HbA1c result > 48mmol/mol
2: Upon diagnosis refer and ensure your patient attends the **DESMOND** education programme **within 6 months of diagnosis**. Patients are more likely to attend if they understand the value of the course, and are **actively encouraged to attend by their Health Care Professional looking after them.**
3: Patients should have an appointment with a dedicated diabetes Dietitian within 1 month of diagnosis.
4: A weight loss target of 3% should be established upon diagnosis and re-enforced at each review, and importantly again at each 'step' of the algorithm.

5: STEP 1: First line treatment in the vast majority of patients should be with Metformin either standard or modified release preparations.
6: If gross osmotic symptoms are present at diagnosis (and type 1 diabetes has been excluded via urine or blood ketone tests); a Sulphonylurea such as Gliclazide should be initiated along with rapid review within 2 weeks.
7: Three monthly patient reviews should occur – HbA1c check, along with re-enforcement of lifestyle changes (attendance to DESMOND programme and dedicated dietitain). Check adherence to medication & potential side effects

8: STEP 2: if HbA1c > 48mmol/mol. Follow either the Traditional or Patho-physiological pathways to address your patients' needs. Re-enforce lifestyle. Target HbA1c at this point is less than 53mmol/mol, but individualise.
8a: Standard/Traditional Pathway - Add in Sulphonylurea to current Metformin.
8b: Alternative Pathway – Add in one of the newer agent to current Metformin depending on individual patient specification – hypoglycaemia risk, Co-morbidities: heart failure, renal function, osteoporosis, maculopathy, weight
9: See point 7. Ensure all agents that are ineffective in lowering HbA1c are stopped.

10: Step 3: Injectable Therapy required if HbA1c > 58mmol/mol and limited further to be gained from greater lifestyle intervention, or other oral agents have been consider and dismissed, or tired and have been unsuccessful.
Follow the Traditional or Patho-physiological pathways. Target HbA1c less than 58mmol/mol but individualise.
10a: Traditional Pathway: Metformin + SU and add in Basal Human Insulin
10b: Alternative pathway for patients with BMI > 35kg/m^2 introduction of GLP-1RA to MF + (SU or TZD)
10c: Combination oral therapies. Ensure previous agents unsuccessful in HbA1c reduction is documented & stopped.
Sensible cost effective prescribing when insulin is unacceptable should include MF + SU + TZD & either DPP4i OR SGLT2i.

Traditional Oral Agents

- **Metformin (MF)**
- **First line treatment in all patients with type 2 diabetes**

- Tablets: 500mg or 850mg
- Dose Regime: once daily initially increasing to twice daily after a week then to three times a day
- With or after food commence with main meal. Usual maximum dose 2g/day
- Trial of Slow Release (SR) preparation in those patients with GI intolerance to standard preparations.

- **Side effects:**
- Nausea, loose motions, gastrointestinal disturbance, B12 deficiency.
- **Contra–indications**:
- Renal Impairment
- Review dose if eGFR less than 45 ml/min/1.73m^2
- **STOP** if eGFR less than 30ml/min/1.73m^2
- Significant heavy alcohol consumption, Risk of Lactic Acidosis, Active Acute Heart Failure, Significant acidosis of any cause

- **Re-enforce Sick Day Rules** during ill health leading to potential volume depletion to avoid Acute Kidney Injury.

- **HbA1c reduction ~ 1 – 2%**

- **Metformin can be added to**
  Sulphonylurea (SU)
  Thiazolidinedione (TZD),
  DPP4 inhibitors (DPP4i)
  GLP-1 analogues (GLP- 1RA) and
  Sodium Glucose Co-transporter inhibitor (SGLT2i)
  Any Insulin regimen

- **Sulphonylureas (SU)**
- Examples: Gliclazide, Glimepiride

- **Indications:**
- Monotherapy in patients with type 2 intolerant of MF
- Where rapid improvement in or hyperglycaemic symptoms required, due to significant osmotic symptoms.
- Combination treatment with MF, TZD, or GLP-1RA, DPP4 inhibitors or SGLT2i
- Combination treatment with long acting human basal human insulin
- Longer acting SU e.g. Glimepiride are weight neutral

- **Side effects:**
- Nausea, vomiting, hepatic dysfunction, hypoglycaemia (educate patient regarding symptoms and treatment), can occur in combination with (dose of the SU needs to be reduced by half) and TZD
- **Contra-indications:**
- Avoid all long acting SU in the elderly, avoid in significant hepatic and renal dysfunction. SUs are contra-indicated in pregnancy. **AVOID** if eGFR less than 30ml/min/1.73m^2

- **HbA1c Reduction ~ 1.5 – 2%**
- **NOTE:** due to the risk of hypoglycaemia your patient will require regular Blood Glucose Monitoring – especially before driving. Please educate regarding testing and risks
- **Add onto:**
  Metformin, TZD, GLP1RA, SGLT2i
  Human Basal Insulin or pre-mixed insulin regimen.

Traditional Oral Agents

- **Metiglinides**

- **Example**: Repaglinide and Nateglinide

- **Indications:**
- Can be considered as an alternative to SU's in patients with renal impairment eGFR < 30
- In combination with Metformin

- **Side Effects:**
- abdominal pain, diarrhoea, constipation, nausea, vomiting, rash

- **Contraindications:**
- Severe hepatic impairment,
- Not to be prescribed in combination with :-
  SU, TZD, DPP4I, GLP-1RA, or SGLT2i.

- **Dosing regime:**
- Repaglinide 500mcg 30mins before food/meal, max 4mg as a single dose. Total daily dose 16mg. Increase at weekly intervals depending on response.

- Netaglinide: 60mg 30mins before food/meal, daily max 180mg tds

- HbA1c reduction ~ 6mmol/mol (0.5 – 1%)

- **Thiazolidinedione (TZD)**
- Examples: Pioglitazone

- **Indications:**
- Type 2 diabetes with BMI > 25kg/m^2:
- Start at 15 - 30mg daily and titrate to 45 mg daily according to response.
- Dual therapy with MF or SU or DPP4i
- Triple therapy MF + SU + TZD
- Combination with human basal Insulin (Hospital initiation ONLY after performing an Echocardiogram)

- **Side effects:**
- **increased abdominal adiposity, weight gain, precipitation of undiagnosed heart failure, anaemia, increased risk of distal limb fracture due to osteoporosis, hypoglycaemia with SU, hepatic dysfunction (monitor LFTs), macular oedema.
- If any side effects occur: re-assess the safety aspects of continued drug therapy versus changing medication.

- **Contra–indications:**
- Known Cardiac failure, Significant hepatic dysfunction or if your patient is at high risk of fracture.
- **Should NOT** be used in patients with active or a past history of Macula Oedema.
- **Consider** checking BNP to exclude undiagnosed heart failure

- **Reduction in HbA1c 6mmol/mol over a 6 months**

- **Add on to** MF, SU, GLP- 1RA , Human Basal Insulin, SGLT2i (Empa or Cana only)

Newer Oral Agents: DPP4 inhibitors

- **DPP4 Inhibitors (Gliptins)** – this class of agents work through the incretin pathway to improve blood glucose levels

- **Examples:** Sitagliptin, Saxagliptin, Linagliptin, Alogliptin or Vildagliptin
- **Consider discussion with either a GPwSI Diabetes or a Hospital Diabetologist prior to initiation.**
- Dosing regime: Sitagliptin 100mg od, Saxagliptin 5mg od, Linagliptin 5mg od
- **NOTE:** Dose reduction required in renal failure with some agents in this class. See BNF for each drug

- **AVOID** in pregnancy and breastfeeding

- **Indications:**

  In addition to MF, TZDs or SU

  If HbA_{1c} > 58 mmol/mol (7.5%) and BMI > 27kg/m^2

  Ideal role – low risk of hypoglycaemia and weight neutrality

- **Side effects**:
- increased digoxin levels. Gastro- Intestinal disturbances, peripheral oedema, osteoarthritis pain, nasopharyngitis and upper respiratory tract infection.
- **Cautions**
- Renal Impairment serum Creatinine > 150mmol/L or eGFR < 30.
- no dose reduction required for Linagliptin in renal failure. See BNF for further advice on prescribing.
- **Contraindications**
- Acute Pancreatitis, Pregnancy & Breast feeding.
- **AVOID** prescribing with GLP1-RA

- **Discontinue if reduction** in HbA1c is less than 0.5% (6 mmol/mol) after 6 months treatment.

Newer Oral Agents: SGLT2 inhibitors

- **SGLT2 inhibitors –** this class of agents work through the kidney preventing the re-absorption of glucose in an insulin independent action. It is important to **enforce sick day rules** to prevent Acute Kidney Injury when using this class.

- **IMPORTANT: Determine renal function before treatment and periodically thereafter.**
- **AVOID initiation of ANY SGLT2i** if **eGFR below 60ml/min/1.73m^2 as these agents are not effective**
- **AVOID initiation or STOP agent if eGFR less than 45ml/min/1.73m^2**
- **CAUTION is advised if** prescribing SGLT2i in patients already taking Loop or Thiazide diuretics due to the high risk of volume depletion and Acute Kidney Injury. Consider stopping the diuretic prior to initiation.

- **Examples:** Dapagliflozin 10mg od , Empagliflozin 10mg or 25mg od or Canaglifloxin 100mg or 300mg od
- **Consider discussion with either a GPwSI Diabetes or a Hospital Diabetologist prior to initiation.**

- **Indication**:
- If HbA_{1c} > 58mmol/mol (7.5%) and BMI > 27kg/m^2
- For effective weight loss targets re-enforce lifestyle changes and refer to local dietetic services on – initiation
- Dual therapy regimen in combination with MF
- Triple therapy – add onto MF + SU (consider reducing SU dose potentially by half to prevent hypoglycaemia)
- In combination with human Insulin with or without other anti-diabetic drugs.

- **SGLT2i SHOULD NOT be prescribed with GLP-1RAs**.
- **AVOID in pregnancy and breastfeeding**

- **Side Effects: ****Genital infections, UTI, Volume depletion during acute illness or with diuretic, Hypotension, (warn patient of potential risk of dizziness), Euglycaemic Ketoacidosis, Osteoporosis (increased fracture risk).
- **Discontinue if reduction** in HbA1c is less than 0.5% (6 mmol/mol) after 6 months treatment.
- **Add onto**: MF, SU, (TZD) + Human Basal Insulin – seek specialist advice

Newer Injectable Agents: GLP-1RA

- **NOTE:** approximately 25 – 33% of patients **will fail to respond** to GLP1-RA therapy, hence on commencement – please use a short acting agent with the lowest acquisition costs. Evaluate at 3 & 6 months – **ONLY continue** if NICE criteria achieved – either continue current agent or convert to a longer acting preparation.
- Short acting preparations will predominately address postprandial hyperglycaemia.
- Thereafter longer acting agents will maintain and improve HbA1c by predominately improving fasting glucose

- Short Acting agents: Exenatide 5mcg BD increasing to 10mcg BD or Lixisenatide 10mcg OD increasing to 20mcg OD
- Intermediate Acting agents – Liraglutide 0.6mg OD increasing to 1.2mg OD (**NOTE** 1.8mg OD is **NOT** advocated in Sunderland)
- Long Acting Weekly agents: Exenatide LAR 2mg once weekly or Dulaglutide 0.75mg 0r 1.5mg once weekly

- **NICE criteria:** Add as part of triple therapy **ONLY if BMI is ≥ 35kg/m^2** in people of European descent (adjust for ethnic groups) and there are specific psychological or medical problems associated with high body weight, or BMI<35kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other co-morbidities.
- **Consider discussion with either a GPwSI Diabetes or a Hospital Diabetologist prior to initiation.**
- Can be considered in dual therapy with MF; Can be considered in dual therapy with a SU if **EITHER** MF contraindicated or not tolerated, OR in combinations of SU &TZD; or SU & DPP-4 inhibitors are contra-indicated or not tolerated
- **NOTE**: only Liraglutide and prolonged release Exenatide LAR considered by NICE for dual therapy.

- **Side effects:** GI disturbance (especially nausea) ~ 30% of patients associated with weight loss, acute pancreatitis
- **Renal Failure**: dose adjustment or cessation required if eGFR reduced/declining for some GLP -1RA. See BNF
- **AVOID** in pregnancy and breastfeeding.

- GLP-1RA used in combination with Human Basal Insulin **ONLY** in specialist care setting.
- **Co-prescribing with Pre-Mixed insulin is NOT recommended and is off license**
- **GLP-1RA should NOT be prescribed with DPP4 inhibitors** as both work through the same (Incretin) pathway
- **GLP-1RA should NOT be prescribed with SGLT2 inhibitors** - an expensive combination with increased risk of volume depletion

- **STOP IF** reduction in HbA1c is less than 1% (11 mmol/mol) **and** there is less than 3% weight loss after 6 months.
- **(NOTE**: Only HbA1c reduction required for patients' on dual therapy)

Injectable Therapies: Insulin

- Patients with type 2 diabetes will require the introduction of insulin at some point in their disease
- **Indications:**
- Progression of disease due to Beta cell failure
- Hyperglycaemia induced by steroids (long course)
- Pre – Operative care (HbA1c > 69mmol/mol or 8.5%)

- **Treatments:**
- **Human Basal Insulin:** once or twice a day - in conjunction with oral therapies (provided they are effective)
- **Examples:** Human Insulatard®, Humulin I®, Insuman Basal®
- Usually initiated due to progression of disease – consider when HbA1c > 69mmol/mol or earlier if alternative therapies ineffective – refer to community DSN or CHS
- **Pre- Mixed Human Insulin:** Twice a day (with breakfast and evening meal)
- **Examples:** Humulin M3®, Insuman Combo 25® – stop SU, continue MF
- Patient symptomatic from high blood glucose levels
- Short history of diabetes
- BMI < 25kg/m^2 (consider alterative diagnosis such as type 1 diabetes – check Anti GAD antibodies)
- HbA1c > 75mmol/mol (9%)

- **Long Acting Analogue Insulin** (see overleaf for information on Biosimilar insulin)
- **Examples:** Insulin Lantus Glargine ® (once a day – midday) or Insulin Levemir Detemir ® (morning & teatime)
- **Indications:**
- Patients with problematic hypoglycaemia (ensure your patient is not on a SU)
- Elderly patients requiring community/district nurse support
- **NOTE:** Basal Bolus Regime is **NOT** routinely used in the management of patients with Type 2 diabetes
- **NOTE: High Strength (U200, U300 or U500) insulin should NOT be initiated in the community**

New Injectable Therapies: Biosimilar Insulin

- A Biosimilar preparations called Abasaglar® is now available, a Basal insulin which is biologically similar in action to Insulin Lantus Glargine®. Other Biosimilar preparations will follow hence **safe, clear prescribing is essential.**

- **Indications:** for Biosimilar insulin to be used only in
  - New patients
  - Patients with suboptimal control where a review of therapy is being considered.
- **Existing patients should continue to receive Insulin Lantus®.**
- **Patients should <u>NOT</u> be routinely switched between brands**

- **Prescribing:** It is essential that patients stay on the same brand. All prescribing should be by Brand Name.
- **Recommendations for Primary Care:** All practices search for any patients currently prescribed insulin Glargine generically and change to the existing branded product, Lantus® before Abasaglar® becomes available, to avoid later confusion.

- **Dispensing**: Pharmacists should dispense the brand ordered and not substitute.
  If a brand is not specified the prescription needs to be returned to the prescriber for this to be added.
  Please note that pharmacists will not dispense insulin Glargine unless prescribed by brand as they are not authorised to amend prescriptions.

- **Administration / Record keeping:** It is important that a record is kept within the patient's notes of the brand used. This is to facilitate reporting of adverse effects.
- **ALL Communications with GP/Health Care Professionals should provide brand details of the product used**.
- **Adverse reactions:** (suspected or established) should be documented on yellow card reports to the MHRA.

- **NOTE: Only limited information is available on the safety of this insulin in Pregnancy and Breastfeeding.**
- **Biosimilar insulin should NOT be routine initiated in the community setting until greater safety data and communication structure is established.**

- **Key Points on the Management of Patients with T2DM**

- Diet, calorie reduction, weight loss and increased physical activity along with smoking cessation and a low salt diet remain the cornerstone of of treatment and should be asked about, assessed and enforced at each 3 monthly review.

- Ensure **ALL** cardiovascular risk factors are addressed effectively in all patients.

- **HbA1c targets should be individualised** based on both patient, disease features and co-morbidities – this will determine the best glucose lowering agent to be prescribed.

- **Metformin remains the drug of first choice**

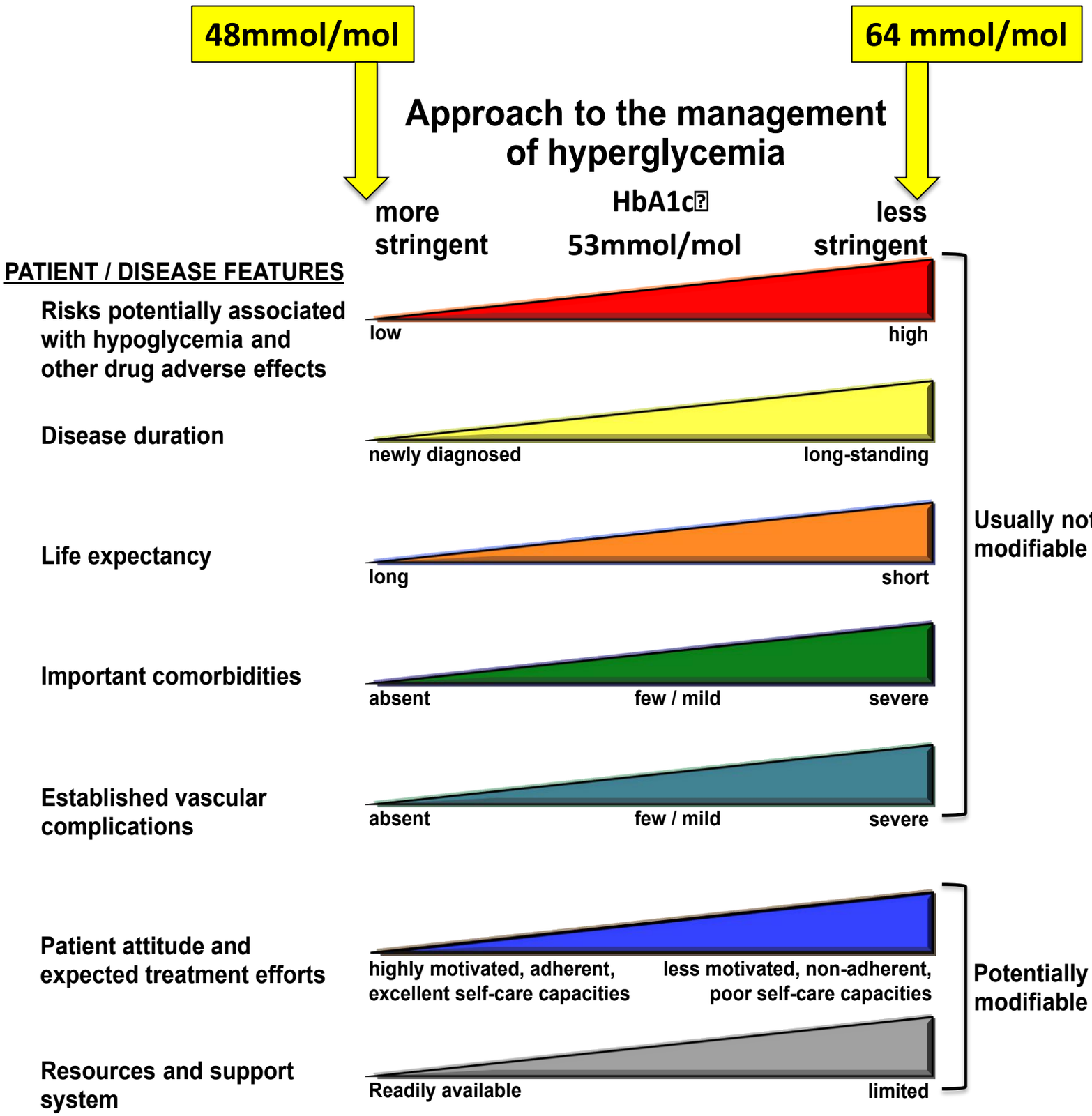
- **After MF:** there is limited data as to the next best agent. Combination therapy of MF plus another 1 or 2 oral agent(s) will be required, thereafter an injectable agent will be needed to achieve targets.

- Additional therapies should be added in as part of a shared decision making process in conjunction with the patient where possible.

- Ensure **REGULAR** 3 and 6 monthly clinical reviews occur. Assess compliance and concordance of lifestyle and medication.

- Medication review – **ONLY** continue if NICE criteria are met for the class.

Modulation of the intensiveness of glucose lowering therapy in T2DM



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442