GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH TO AVOID **CLINICAL INERTIA** FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY) REASSESS AND IF Hba. Above target proceed as below MODIFY TREATMENT REGULARLY (3-6 MONTHS) NO ESTABLISHED ASCVD OR CKD WITHOUT ESTABLISHED ASCVD OR CKD **ASCVD PREDOMINATES** HF OR CKD PREDOMINATES COMPELLING NEED TO MINIMISE WEIGHT **EITHER GAIN OR PROMOTE WEIGHT LOSS** COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA COST IS A MAJOR ISSUE9-10 OR PREFERABLY SGLT2i with evidence of reducing EITHER/ HF and/or CKD progression in SGLT2i with OR GLP-1 RA with CVOTs if eGFR adequate3 GLP-1 RA proven CVD DPP-4i GLP-1 RA SGLT2i² TZD good efficacy SGLT2i2 SUS TZD10 benefit1. with proven for weight loss8 CVD benefit¹ if eGFR If SGLT2i not tolerated or adequate2 contraindicated or if eGFR less If HbA, If HbA. If HbA. If HbA. than adequate2 add GLP-1 RA If HbA, above target If HbA, above target above target above target above target above target with proven CVD benefit1 GLP-1 RA SGLT2i2 SGLT2i2 SGLT2i2 If HbA, above target OR GLP-1 RA with If HbA, above target DPP-4i TZD10 SU⁶ OR OR DPP-4i SGLT2i2 good efficacy TZD TZD OR OR for weight loss⁸ If further intensification is required or TZD GLP-1 RA Avoid TZD in the setting of HF patient is now unable to tolerate T Choose agents demonstrating CV safety: GLP-1 RA and/or SGLT2i, choose Consider adding the other class If HbA, above target If HbA, above target If HbA, above target agents demonstrating CV safety: with proven CVD benefit1 · Consider adding the other class DPP-4i (not saxagliptin) in the setting (GLP-1 RA or SGLT2i) with proven Continue with addition of other agents as outlined above . Insulin therapy basal insulin with of HF (if not on GLP-1 RA) If triple therapy required or SGLT2i CVD benefit lowest acquisition cost and/or GLP-1 RA not tolerated or Basal insulin4 DPP-4i if not on GLP-1 RA SU contraindicated use regimen with Basal insulin⁴ If HbA, above target Consider DPP-4i OR SGLT2i with lowest risk of weight gain TZD⁵ lowest acquisition cost¹⁰ **PREFERABLY** SUS Consider the addition of SU⁶ OR basal insulin: DPP-4i (if not on GLP-1 RA) based on weight neutrality Choose later generation SU with lower risk of hypoglycaemia Consider basal insulin with lower risk of hypoglycaemia? If DPP-4i not tolerated or 1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest Low dose may be better tolerated though less well studied for CVD effects contraindicated or patient already on evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence 6. Choose later generation SU with lower risk of hypoglycaemia GLP-1 RA. cautious addition of: modestly stronger for empagliflozin > canagliflozin. 7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin SU⁶ • TZD⁵ • Basal insulin 2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR 8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide for initiation and continued use 9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower 3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD priority to avoid weight gain or no weight-related comorbidities) 10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more progression in CVOTs expensive and DPP-4i relatively cheaper

4. Degludec or U100 glargine have demonstrated CVD safety