Therapeutic Inertia

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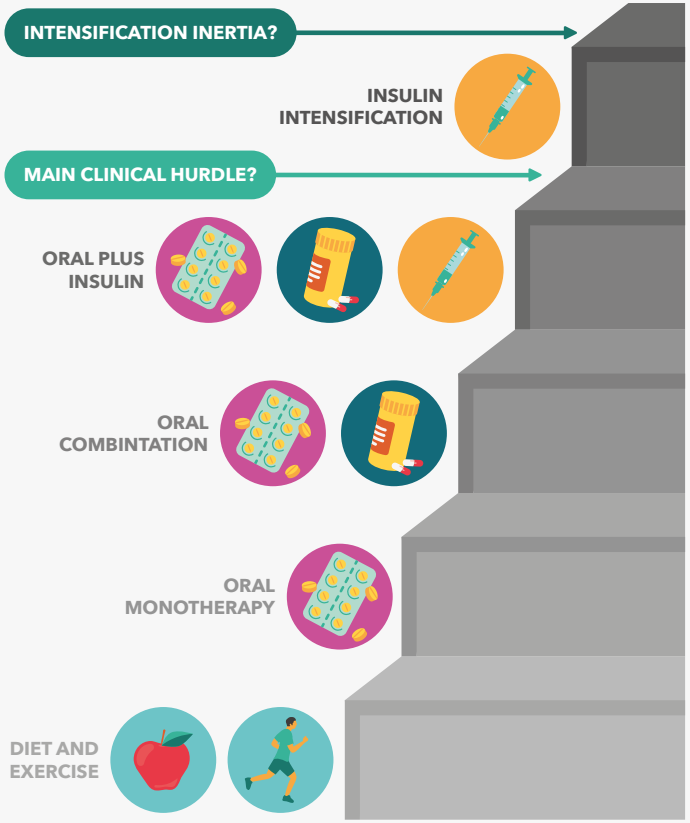
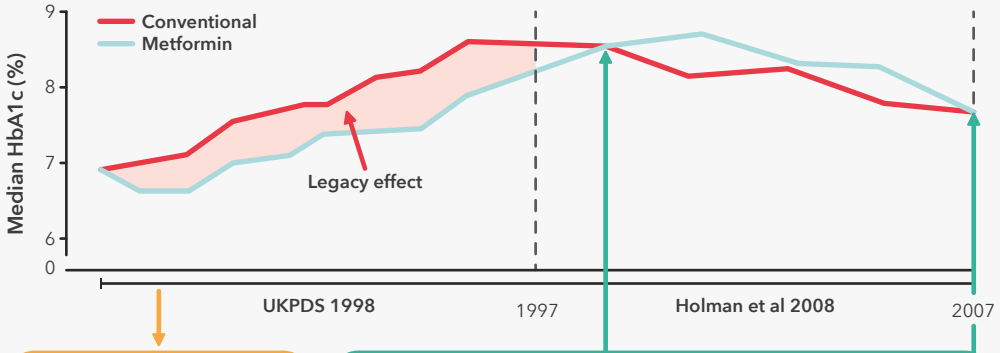
What is therapeutic inertia?

Despite the importance of maintaining good glycaemic control "**therapeutic inertia**" – the "***failure to advance therapy or to de-intensify therapy when appropriate to do so***" – has led to poor glycaemic control and worse microvascular, macrovascular and mortality outcomes globally[1-3]



Therapeutic inertia is present throughout the disease paradigm, from the first OAD to the initiation of insulin, and even insulin intensification – so-called "**intensification inertia**"

Impact of early glycaemic control



UKPDS showed early glycaemic control led to microvascular benefits[3]

In the post-trial follow-up differences in HbA_{1c} was lost after first year but there were further reductions in incident of any complication[4]

24% in microvascular complications

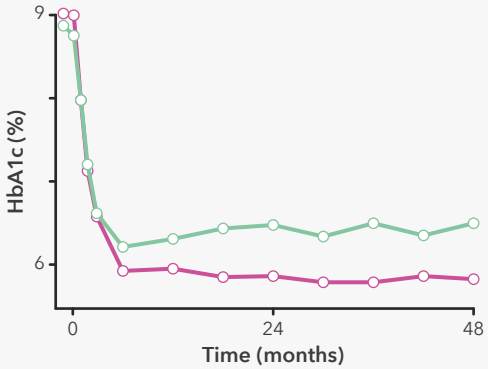
15% in MI

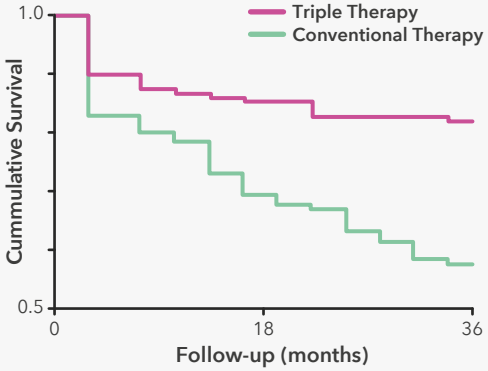
13% in all-cause mortality

Adapted from Holman RR et al. 2008; UKPDS 33. 1998

Long-term studies have shown that **early glycaemic control** results in better vascular and mortality outcomes at later stages, the so-called "**legacy effect**"[3-5]

The **EDICT** study compared early triple therapy (metformin/pioglitazone/exenatide) with conventional therapy (metformin followed by sequential addition of sulfonylurea and insulin glargine) in newly diagnosed, drug-naïve T2DM patients





Adapted from DeFronzo RA, et al. 2016

Compared with conventional therapy, triple therapy led to:

- Significantly greater HbA_{1c} reduction
- More durable HbA_{1c} lowering
- Significant improvement in vascular and mortality outcomes at 3 years

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An early intensive approach has been adopted by many guidelines

ADA/EASD 2018 guideline recommended SGLT-2is and GLP-1 RAs as add-on therapies to metformin in patients with established ASCVD or CKD[4]

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} REMAINS ABOVE TARGET PROCEED AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

GLP-1 RA with proven CVD benefit

EITHER/ OR

SGLT2i with proven CVD benefit, if eGFR adequate

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

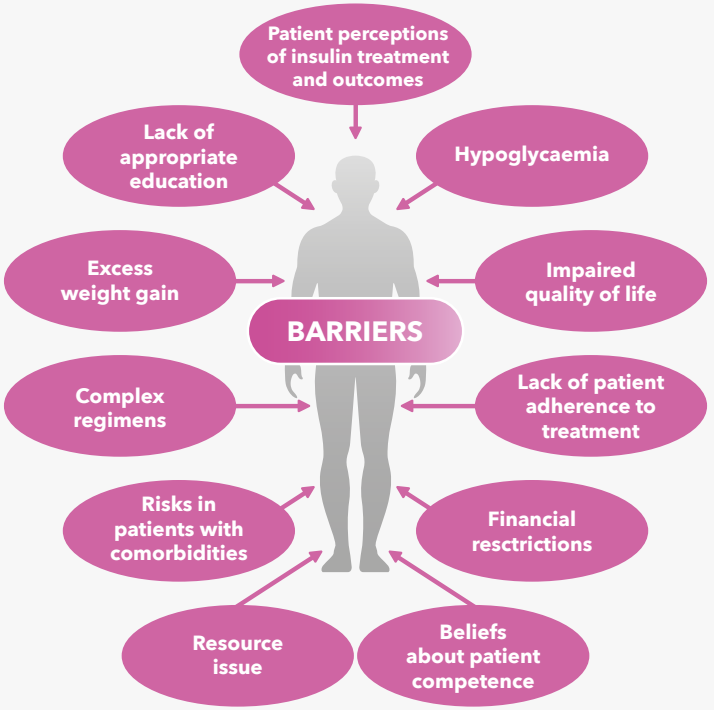
OR

If SGLT2i not tolerated or contraindicated or it eGFR less than adequate add GLP-1 RA with proven CVD benefit

Adapted from Davies MJ et al. 2018

How to mitigate therapeutic inertia?

Therapeutic inertia results from a complex interplay of patient-, clinician-, and health system–related barriers [7]



Solutions to overcoming therapeutic inertia include **individualising therapies** and **interventions** including:

1. Self-examination of performance by HCPs
2. CME on new and evolving therapies
3. Use of allied HCPs as case managers[8]

Abbreviations: ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CME, continued medical education; CVD, cardiovascular disease; CVE, cardiovascular endpoint; CVOT, cardiovascular outcome trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; EDICT, Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HbA_{1c}, haemoglobin A_{1c}; HCPs, healthcare professionals; HF, heart failure; IT, treatment intensification; MI, myocardial infarction; OAD, oral antihyperglycaemic drug; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2DM, type 2 diabetes mellitus; UKPDS, The UK Prospective Diabetes Study

References: **1.** Paul S, et al. *Cardiovasc Diabetol* 2015;14:100. **2.** Khunti K et al. *Prim Care Diab* 2017;11:105-106. **3.** UKPDS 33. Lancet. 1998; 352: 837–853. **4.** Holman RR et al. *N Engl J Med*. 2008; 359: 1577–1589. **5.** DeFronzo RA et al. 52nd EASD Annual Meeting 2016, Munich, Germany; Abstract and poster presentation 794. Available at: www.easdvirtualmeeting.org, last accessed October 2021. **4.** Holman RR et al. *N Engl J Med*. 2008; 359: 1577–1589. **5.** DeFronzo RA et al. 52nd EASD Annual Meeting 2016, Munich, Germany; Abstract and poster presentation 794. Available at: www.easdvirtualmeeting.org, last accessed 01 March, 2017. **6.** Davies MJ et al. *Diabetes Care* 2018. Sep; dci180033. **7.** Zafar A et al. *Diabetic Med* 2015;32:407-413. **8.** Zafar A, et al. *Prim Care Diabetes*. 2010;4:203-7.