Cardiovascular and major journals

Insulin provision therapy associated with higher mortality than insulin sensitising therapy in older people

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The prevalence of type 2 diabetes is rapidly growing in older people; indeed some estimates suggest that the number of adults ≥75 years of age with type 2 diabetes is expected to increase by 449% from 2005 to 2050, compared with a 220% increase in adults aged 65–74 and a 200% increase in adults <65 years. This growing burden of type 2 diabetes is associated with a significant burden of cardiovascular disease, with as many as 68% of people with type 2 diabetes >65 years of age dying of heart disease. Despite this, treatment strategies for older adults with type 2 diabetes are largely based on opinion rather than definitive evidence.

With these issues in mind, this study compared the effects of insulin provision (IP) therapy (insulin and insulin secretagogues) versus insulin sensitising (IS) therapy (biguanides and thiazolidinediones) for glycaemic control in older (≥75 years) and younger (<75 years) adults with type 2 diabetes and established stable ischaemic heart disease. Adults enrolled in the Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI-2D) trial were studied. All those enrolled with type 2 diabetes and ischaemic heart disease were randomised twice: (1) between revascularisation plus intensive medical therapy versus intensive medical therapy alone; and (2) between IP versus IS therapies. The primary endpoint was all-cause-mortality over 5-year follow-up. In this substudy, outcomes related to IP versus IS therapies were assessed in relation to age.

Compared to younger subjects, the older cohort had lower body mass index, higher diuretic use, worse kidney function and increased history of heart failure. Within the older cohort, the IP and IS subgroups were similar in respect to baseline cardiovascular risk factors, medications and coronary artery disease severity.

During follow-up, the older subjects receiving IP therapy had higher cardiovascular mortality than those receiving IS therapy (16% vs 11%, $P=0.040$). Using Cox proportional hazards analysis, the older IP subjects were at increased risk for all-cause mortality (hazard ratio, 1.89; confidence interval, 1.1–3.2; $P=0.020$). No mortality difference between IP and IS therapies was observed in those <75 years of age.

This study therefore illustrates that older adults with type 2 diabetes and ischaemic heart disease who received IP therapy had increased risks for all-cause mortality and cardiovascular events compared to those who received IS therapy. Additionally, no differences in treatment effects were evident for adults aged <75 years, implying that optimal therapeutic strategies for older adults may differ from those in younger people.

Based on this study, insulin-providing therapy in older people with type 2 diabetes and ischaemic heart disease may be associated with adverse outcomes. There is potential biological plausibility related to these observations, specifically around hypoglycaemia and its link with cardiovascular events, with the elderly being particularly vulnerable to the consequences of hypoglycaemia.

While the results of this study provide some insights into potential treatment strategies for older people with type 2 diabetes, it has a major limitation – namely that newer therapies such as SGLT2 inhibitors and GLP-1 receptor agonists are not represented within the analysis. Additionally the cohort comprises a relatively small number of >75-year-olds (around 8% of the total population), while there are limited data on metabolic factors or hypoglycaemic episodes, which would be extremely useful in understanding possible mechanisms underlying these data. Nevertheless, this study clearly suggests that there may be significant outcome differences related to different therapeutic strategies in younger and older people with type 2 diabetes. ■

Int J Cardiol

Insulin provision and mortality in older adults with diabetes and heart disease

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 There are no clear optimal glycaemic control strategies in very old adults with diabetes and stable ischaemic heart disease (SIHD). This study compared the effectiveness of insulin provision (IP) therapy with insulin sensitising (IS) therapy in older (≥75 years) and younger (<75 years) adults with T2D and SIHD.

2 Adults in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial were randomised twice: (1) between revascularisation plus intensive medical therapy versus intensive medical therapy alone; and (2) between IP versus IS therapies. All-cause mortality over 5-year follow-up was the primary endpoint.

3 There were 2368 patients with SIHD and T2D, of which 182 were ≥75 years. The older group had higher diuretic use, lower body mass index, poorer kidney function and increased history of heart failure. The older IP and IS therapy subgroups had similar baseline cardiovascular risk factors, coronary artery disease severity and medications.

4 Cardiovascular mortality was higher in the older IP versus the older IS subgroup during follow-up (16% vs 11%); the IP subgroup was at increased risk for all-cause mortality ($P=0.020$). No difference in mortality between IP and IS therapies was seen in the younger group.

5 IP therapy may be related to higher mortality than IS therapy in people ≥75 years with T2D and SIHD.

Damluji AA, Cohen ER, Moscucci M et al (2017) Insulin provision therapy and mortality in older adults with diabetes mellitus and stable ischemic heart disease: insights from BARI-2D trial. *Int J Cardiol* **241**: 35–40

Circulation

High-sensitivity troponin 1 and CV outcomes in T2D

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care) trial studied the link between change in high-sensitivity troponin 1 (hsTnI) levels and cardiovascular (CV) outcomes.

2 Baseline and 6-month hsTnI levels were measured in 3808 T2D patients with HbA_{1c} 48–97 mmol/mol (6.5–11%) – or 53–97 mmol/mol (7%–11%) if on insulin – and recent acute coronary syndrome (15–90 days before randomisation). The primary endpoint was CV death, myocardial infarction or stroke. The secondary endpoint was CV death or heart failure.

3 At baseline, hsTnI was detectable in 93% of patients and the >99th percentile upper reference limit (PURL) in 16%.

4 Increasing hsTnI at baseline and 6 months significantly increased CV event risk at 24 months (both $P<0.001$). The risk of CV events was lowest in patients with undetectable baseline and 6-month hsTnI levels.

5 The risk of primary endpoints was significantly increased in stable patients with hsTnI ≥99th PURL at 6 months versus patients with hsTnI <99 PURL ($P<0.001$).

6 Alogliptin did not affect the risk of CV events in patients with high baseline hsTnI compared with placebo.

7 Dynamic or persistently raised hsTnI levels were found in a large proportion of patients with T2D and no clinically-recognised events. In people with T2D, hsTnI may have a role in preventive strategies based on risk.

Cavender MA, White WB, Jarolim P et al (2017) Serial measurement of high-sensitivity troponin I and cardiovascular outcomes in patients with type 2 diabetes mellitus in the EXAMINE trial (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care). *Circulation* **135**: 1911–21

JAMA

Waist-to-hip ratio associated with T2D and CHD

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 Observational studies have linked abdominal adiposity with T2D and coronary heart disease (CHD).

2 This study tested the association of a polygenic risk score for waist-to-hip ratio (WHR) adjusted for body mass index (BMI) with T2D and CHD through blood lipids, blood pressure and glycaemic phenotypes.

3 Mendelian randomisation analysis of case–control and cross-sectional data sets (n=434 140) was used to test the 48 single-nucleotide polymorphism polygenic risk score, which measured genetic predisposition towards abdominal adiposity.

4 Estimates of T2D and CHD were derived from two genome-wide association studies (n=334 126). Outcomes were the presence of CHD and T2D.

5 A one-standard deviation increase in WHR adjusted for BMI mediated by the polygenic risk score was associated with a 27 mg/dL higher triglyceride level, 4.1 mg/dL higher 2-hour glucose level and 2.1 mmHg higher systolic blood pressure (all $P<0.001$).

6 A one-standard deviation genetic increase in WHR adjusted for BMI was associated with a higher risk of T2D (odds ratio, 1.77) and CHD (odds ratio, 1.46).

7 People were at an increased risk of T2D and CHD if they had a genetic predisposition towards a higher WHR when adjusted for BMI.

8 Evidence supports a causal association between abdominal adiposity and T2D and CHD.

Emdin CA, Khera AV, Natarajan P et al (2017) Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes and coronary heart disease. *JAMA* **317**: 626–34

J Intern Med

Glycaemic control and excess risk of stroke in T1D

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 The results of a growing number of studies in the past decade have indicated that T1D is a risk factor for stroke. This study aimed to estimate the excess risk of stroke in relation to glycaemic control in people with T1D.

2 Adults with T1D registered in the Swedish National Diabetes Register between 1998 and 2001 (n=33 453) were compared with age- and sex-matched controls from the general population (n=159 924). Cox hazard regression was used to estimate the risks of haemorrhagic, ischaemic and all types of stroke.

3 Compared to 0.7% of controls, 2.3% of T1D patients were diagnosed with stroke. The multiple adjusted hazard ratios for T1D patients versus controls were 3.29 for ischaemic stroke and 2.49 for haemorrhagic stroke.

4 The risk of both types of stroke increased incrementally with increasing HbA_{1c}.

5 The risks of both ischaemic and haemorrhagic stroke were markedly increased for HbA_{1c} ≥83 mmol/mol (≥9.7%); the multiple-adjusted hazard ratios were 7.94 for ischaemic stroke and 8.17 for haemorrhagic stroke.

6 Ischaemic stroke risk was significantly increased with HbA_{1c} within the target range (≥52 mmol/mol [≥6.9%]; multiple-adjusted hazard ratio, 1.89).

7 People with T1D are at increased risk of stroke, and this risk increases with poor glycaemic control.

Hedén Ståhl C, Lind M, Svensson AM, et al (2017) Glycaemic control and excess risk of ischaemic and haemorrhagic stroke in patients with type 1 diabetes: a cohort study of 33 453 patients. *J Intern Med* **281**: 261–72

"There may be significant outcome differences related to different therapeutic strategies in younger and older people with type 2 diabetes."