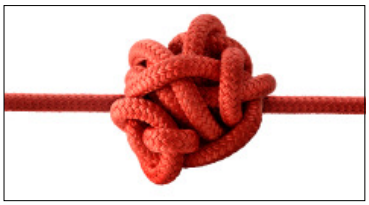
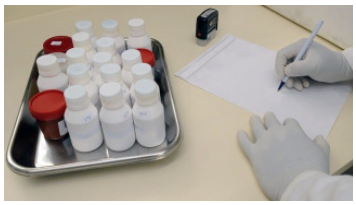
research

Insulin choice in children with diabetes p 59



Life events and cardiovascular disease p 60



Sotagliflozin in type 1 diabetes p 62

ORIGINAL RESEARCH Pragmatic randomised controlled trial and economic evaluation

Continuous subcutaneous insulin infusion versus multiple daily injection regimens in children and young people at diagnosis of type 1 diabetes

Blair JC, McKay A, Ridyard C, et al; for the SCIPI investigators

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Find this at: http://dx.doi.org/10.1136/bmj.l1226

Study question Do newly diagnosed paediatric patients with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII) have superior glycaemic control compared with patients treated with multiple daily injections (MDI), one year after diagnosis?

Methods This trial recruited 294 participants (293 were included in intention-to-treat analyses; CSII, n=144; MDI, n=149) aged 7 months to 15 years with a new diagnosis of type 1 diabetes from 15 NHS diabetes services in England and Wales. Participants were randomised, stratified by age and treating centre, to start randomised treatment within 14 days of diagnosis. Starting insulin doses were standardised, and titrated according to local protocols. The primary outcome was glycaemic control at 12 months. Secondary outcomes were percentage of patients with glycated haemoglobin (HbA_{1c}) within the national target range, incidence of severe hypoglycaemia and diabetic ketoacidosis, change in height and body mass index, insulin requirements, partial remission rate, paediatric quality of life inventory score, and cost utility based on the incremental cost per quality adjusted life year (QALY) gained from an NHS costing perspective.

Study answer and limitations At 12 months, mean HbA_{1c} did not differ significantly between CSII and MDI participants (intention-to-treat analysis: 60.9 *v* 58.5 mmol/mol, mean difference 2.4 (95% confidence interval −0.4 to 5.3), P=0.09). Achievement of HbA_{1c} less than 58 mmol/mol was low among the two groups (46% CSII participants *v* 55% MDI participants; relative risk 0.84 (0.67 to 1.06)). Incidence of severe hypoglycaemia and diabetic ketoacidosis was low in both groups. 54 non-serious and 14 serious adverse events were reported during CSII treatment, and 17 non-serious and eight serious adverse events during MDI treatment. CSII was more expensive than MDI by £1863 (95% confidence interval £1620 to £2137) per patient, with no additional QALY gains. These findings should not be applied beyond the first year of diagnosis, and innovation in CSII technology could facilitate better outcomes in CSII treated patients in the future.

What this study adds During the first year following a diagnosis of type 1 diabetes, no glycaemic control benefit of CSII over MDI was identified. CSII was not cost effective.

Funding, competing interests, and data sharing Funded by the National Institute for Health Research Health Technology Assessment Programme (HTA 08/14/39). See bmj.com for full details of competing interests. The authors are committed to sharing anonymised individual patient data for the purpose of research.

Trial registration Current Controlled Trials ISRCTN29255275; European Clinical Trials Database 2010-023792-25.

Primary and selected secondary outcome measures

	CSII (n=144)	MDI (n=149)	Effect estimate (95% CI)	P value
HbA_{1c} (mmol/mol) at 12 months (primary outcome)*†:				
Intention-to-treat analysis‡	143, 60.9 (58.5 to 63.3)	142, 58.5 (56.1 to 60.9)	2.4 (−0.4 to 5.3)	0.09
Per protocol	87, 60.2 (56.4 to 63.9)	66, 59.3 (55.3 to 63.2)	0.9 (−3.2 to 5.0)	0.67
HbA_{1c} <58 mmol/mol‡§¶	143, 66 (46.2)	142, 78 (54.9)	0.84 (0.67 to 1.06)	0.16
HbA_{1c} <48 mmol/mol‡§¶	143, 22 (15.4)	142, 29 (20.4)	0.75 (0.46 to 1.25)	0.28
Incidence of severe hypoglycaemia‡§	144, 6 (4.2)	149, 2 (1.3)	3.1 (0.6 to 15.1)	0.17
Incidence of diabetic ketoacidosis‡§	144, 2 (1.4)	149, 0	5.2 (0.3 to 106.8)	0.24

*Continuous outcomes presented as total number of participants, adjusted mean (95% confidence interval); adjusted mean difference (95% confidence interval). †Analysis adjusted for randomisation group (age category, fixed effects; centre, random effects).‡Intention-to-treat analysis. §Binary outcomes presented as total number of participants, number (%); relative risk (95% confidence interval). ¶58 mmol/mol was the national target up to August 2015; 48 mmol/mol was the target set in August 2015.

Stress, psychiatric disorders, and cardiovascular disease

ORIGINAL RESEARCH Population based, sibling controlled cohort study

Stress related disorders and risk of cardiovascular disease

Song H, Fang F, Arnberg FK, et al

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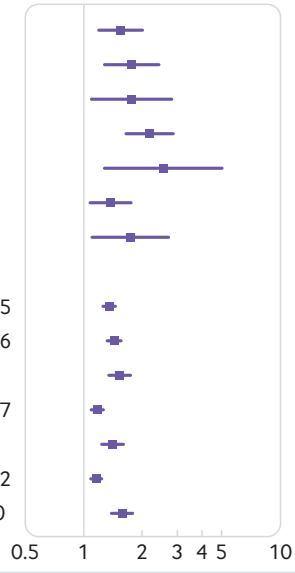
Find this at: http://dx.doi.org/10.1136/bmj.l1255

Study question Are clinically confirmed stress related disorders associated with subsequent risk of cardiovascular disease?

Methods This was a population based, sibling controlled cohort study in Sweden. Through the Swedish National Patient Register, 136 637 patients with a clinical diagnosis of stress related disorders (post-traumatic stress disorder (PTSD), acute stress reaction, adjustment disorder, and other stress reactions) were identified from 1987 to 2013 and compared with 171 314 unaffected full siblings of these patients and 1 366 370 matched unexposed people from the general

Cardiovascular diseases	No of cases in patients/siblings	Hazard ratio (95% CI)	Hazard ratio (95% CI)
<1 year of follow-up			
Ischaemic heart disease	161/193		1.53 (1.18 to 2.00)
Cerebrovascular disease	120/119		1.75 (1.26 to 2.42)
Emboli/thrombosis	61/56		1.75 (1.09 to 2.80)
Hypertensive diseases	168/143		2.15 (1.61 to 2.86)
Heart failure	41/29		2.52 (1.25 to 5.08)
Arrhythmia/conduction disorder	196/215		1.36 (1.08 to 1.72)
Fatal cerebrovascular events	96/66		1.72 (1.10 to 2.68)
≥1 year of follow-up			
Ischaemic heart disease	2121/3525		1.34 (1.25 to 1.44)
Cerebrovascular disease	1417/2006		1.42 (1.31 to 1.55)
Emboli/thrombosis	622/749		1.52 (1.34 to 1.74)
Hypertensive diseases	1531/2567		1.16 (1.08 to 1.26)
Heart failure	609/933		1.39 (1.22 to 1.60)
Arrhythmia/conduction disorder	1975/3222		1.16 (1.08 to 1.24)
Fatal cerebrovascular events	813/1030		1.56 (1.37 to 1.77)



Relative risks of developing different types of cardiovascular disease among patients with any stress related disorder, compared with their full siblings, by time of follow-up (<1 year or ≥1 year)

COMMENTARY Clear evidence now links stress induced disorders such as PTSD to a higher risk of CVD

Well established links now exist between mood disorders such as depression and an increased risk of cardiovascular disease,[1] and a large but somewhat contentious literature links anxiety disorders with cardiovascular disease.[2 3] In contrast, data on the associations between other psychiatric disorders and cardiovascular disease are limited. In the linked paper[4] Song and colleagues report on an elegant population based cohort study, including both sibling controlled and population matched designs, exploring associations between acute psychiatric disorders induced by an acute stressful life event and cardiovascular disease.

In this large study (approximately 130 000 patients with a psychiatric disorder induced by acute stress, such as post-traumatic stress disorder (PTSD), acute stress reaction, or adjustment disorder), the authors found a consistent, significant association between having a

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Stress induced biological mechanisms may drive the link between psychiatric disorder and cardiovascular disease

disorder and future cardiovascular disease events. These associations were strongest in the first year after a diagnosis of a stress induced psychiatric disorder.

One of the great strengths of this study is the sibling controlled design, which allows us to make reasonable assumptions about the similarity of the environment, lifestyles, and health behaviours between people with a disorder and their paired siblings without one. Such assumptions allow inferences about alternative potential pathways linking these disorders to cardiovascular disease.

Combined effect

As the authors say, stress induced biological mechanisms may drive the link between psychiatric disorder and cardiovascular disease. Multiple laboratory studies have identified stress induced physiological changes linked to increased cardiovascular disease.[5 6] More importantly, these stress induced responses are mediated by the presence of a psychiatric disorder.[7 8] Therefore, it seems likely that the experience of the stressful life event and the consequent development of the psychiatric disorder combine to enhance physiological dysregulation and risk of cardiovascular disease.

Reverse causation, however, is another possibility, whereby people with some degree of underlying cardiovascular disease are prone to developing stress related psychiatric disorders. Song and colleagues rightly cite the increased risk of acute outcomes (such as cardiac arrest, acute myocardial infarction, and acute cerebrovascular disease) one year after the psychiatric diagnosis as evidence of a unidirectional association. However, the largest effect size is seen with heart failure less than one year after diagnosis (hazard ratio 6.95, 95% confidence interval 1.88 to 25.68). Heart failure is often a slowly

population. Associations with a primary diagnosis of incident cardiovascular disease—any or specific subtypes (ischaemic heart disease, cerebrovascular disease, emboli/thrombosis, hypertensive diseases, heart failure, arrhythmia/conduction disorder, and fatal cardiovascular diseases)—and 16 individual diagnoses of cardiovascular disease were assessed using hazard ratios derived from conditional Cox models, after control for multiple confounders.

Study answer and limitations

Compared with unaffected full siblings, the hazard ratio for any cardiovascular disease for patients with stress related disorder was 1.64 (95% confidence interval 1.45 to 1.84) during the first year after the diagnosis, with varied estimates among subtypes of cardiovascular disease. Beyond one year, the hazard ratios became lower (any cardiovascular disease: 1.29, 1.24 to 1.34). Analyses within the population matched cohort yielded similar results. Limitations include the absence of information from primary care and late inclusion of outpatient specialist care records.

What this study adds

In the Swedish population, a clinical diagnosis of stress related disorders was significantly associated with higher subsequent risk of multiple types of cardiovascular disease, especially during the first year after the diagnosis. This association was independent of familial background, history of somatic/psychiatric diseases, and psychiatric comorbidities.

Funding, competing interests, and data sharing

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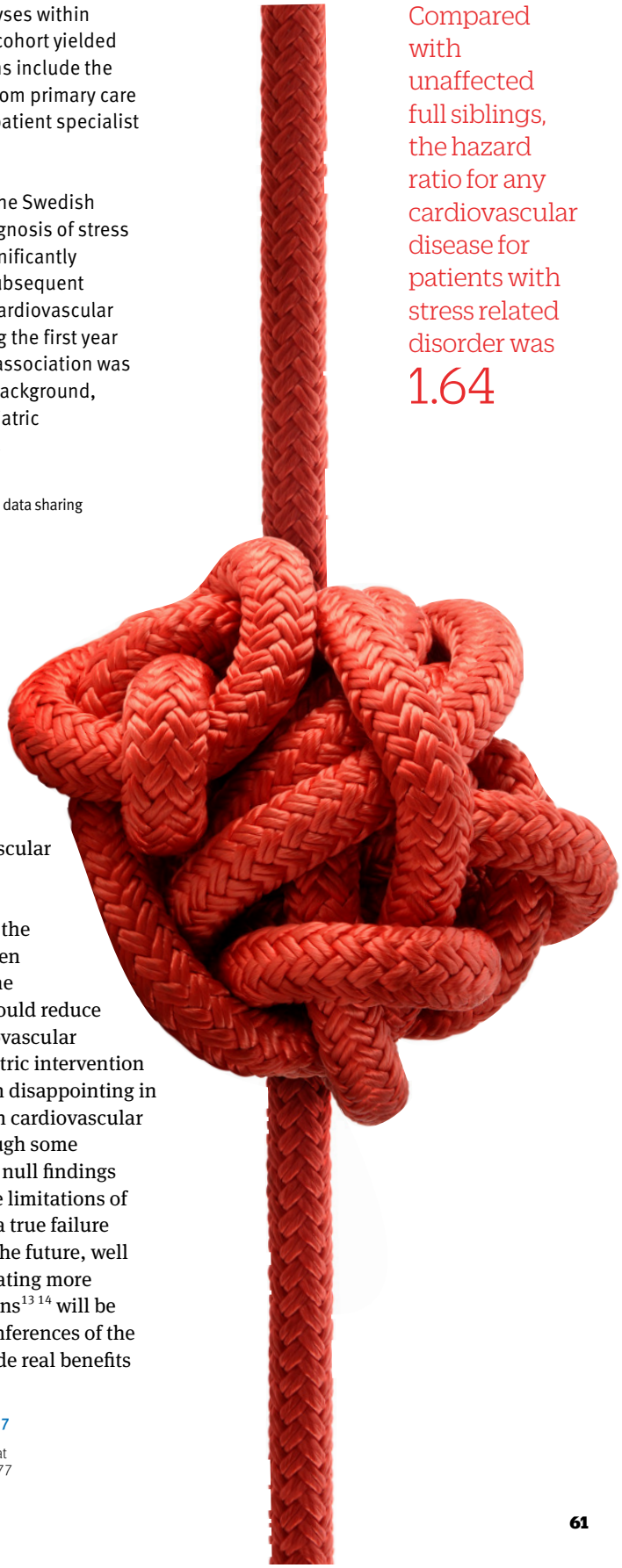
Compared with unaffected full siblings, the hazard ratio for any cardiovascular disease for patients with stress related disorder was 1.64



evolving chronic disease,[9] so reverse causation cannot be ruled out entirely and further studies exploring the potential bidirectional nature of this relation are needed.

Associations with cardiovascular disease are not unique to this cluster of disorders. Evidence also links mood disorders with cardiovascular disease,[1] and some forms of depression may be induced by stress.[10] This raises questions about the extent to which Song and colleagues' findings are unique to recognised stress induced disorders such as PTSD or shared with other psychiatric disorders. The signal that adults with comorbid psychiatric disorders had higher odds of cardiovascular disease events is partial evidence for the synergistic effects of a variety of disorders on risk of cardiovascular disease. The interplay between multiple psychiatric disorders and cardiovascular risk is an area deserving further exploration.[2]

Finally, the ultimate test of an underlying unidirectional relation between acute stress induced psychiatric disorders and cardiovascular disease will be through intervention studies to treat these disorders. If the association is causal then effective treatment of the psychiatric disorder should reduce the risk of future cardiovascular disease events. Psychiatric intervention studies have so far been disappointing in relation to reductions in cardiovascular disease events,[11] although some people suggest that the null findings had more to do with the limitations of the interventions than a true failure of the hypothesis.[12] In the future, well designed studies evaluating more appropriate interventions[13 14] will be critical to confirm the inferences of the new study and to provide real benefits to patients.[12 15]

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Find the full version with references at http://dx.doi.org/10.1136/bmj.l1577

Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes

Musso G, Gambino R, Cassader M, Paschetta E

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Study question
What is the efficacy and safety of the dual sodium glucose cotransporter (SGLT) 1/2 inhibitor sotagliflozin in patients with type 1 diabetes?

Methods
Databases, clinical trial registries, regulatory authority websites, and manufacturer websites were searched for records of randomised controlled trials comparing sotagliflozin with active comparators or placebo in adults with type 1 diabetes up to 10 January 2019. Outcomes were pooled by random effects models, and strength of evidence was summarised by the GRADE approach (grading of recommendations assessment, development, and evaluation).

Study answer and limitations
Of 739 records identified, six randomised placebo controlled trials (n=3238, duration 4-52 weeks) were included. Sotagliflozin reduced levels of glycated haemoglobin (HbA_{1c}; weighted mean difference −0.34% (95% confidence interval −0.41% to −0.27%), P<0.001); fasting plasma glucose (−16.98 mg/dL, −22.1 to −11.9; 1 mg/dL=0.0555 mmol/L) and two hour postprandial plasma glucose (−39.2 mg/dL, −50.4 to −28.1); and daily total, basal, and bolus insulin dose (−8.99%, −10.93% to −7.05%; −8.03%, −10.14% to −5.93%; −9.14%, −12.17% to −6.12%; respectively). Sotagliflozin improved time in range (weighted mean difference 9.73%, 6.66% to 12.81%) and other continuous glucose monitoring parameters, and reduced body weight (−3.54%, −3.98% to −3.09%), systolic blood pressure (−3.85 mm Hg, −4.76 to −2.93), and albuminuria (albumin:creatinine ratio −14.57 mg/g, −26.87 to −2.28). Sotagliflozin reduced hypoglycaemia (weighted mean difference −9.09 events per patient year, −13.82 to −4.36) and severe hypoglycaemia (relative risk 0.69, 0.49 to 0.98). However, the drug increased the risk of ketoacidosis (relative risk 3.93, 1.94 to 7.96), genital tract infections (3.12, 2.14 to 4.54), diarrhoea (1.50, 1.08 to 2.10), and volume depletion events (2.19, 1.10 to 4.36). Initial HbA_{1c} and basal insulin dose adjustment were associated with the risk of diabetic ketoacidosis. A sotagliflozin dose of 400 mg/day was associated with a greater improvement in most glycaemic and non-glycaemic outcomes than the 200 mg/day dose, without increasing the risk of adverse events. The quality of evidence was high to moderate for most outcomes, but low for major adverse cardiovascular events and all cause death. The relatively short duration of trials prevented assessment of long term outcomes.

What this study adds In type 1 diabetes, sotagliflozin improves glycaemic and non-glycaemic outcomes and reduces hypoglycaemia burden. The risk of diabetic ketoacidosis could be minimised by appropriate patient selection and protocols to adjust the basal insulin dose.

Funding, competing interests, and data sharing No funding or competing interests declared. Data are available from the corresponding author on reasonable request.