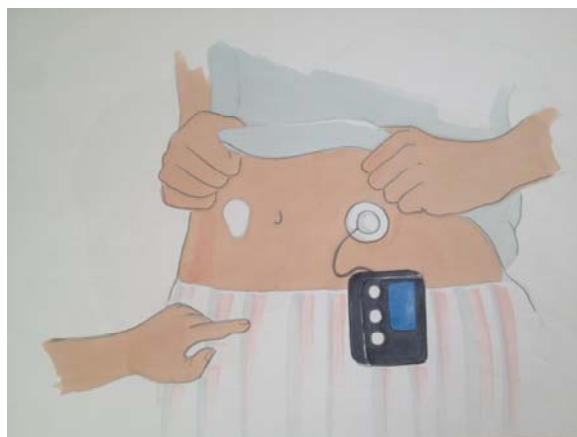# Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study

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RESEARCH

Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study

Isabelle Steineck,[1] Jan Cederholm,[2] Björn Eliasson,[3] Ann-Marie Svensson,[4] Björn Zethelius,[5,6] Tarik Avdic,[4] Araz Rawshani,[4] Katarina Eeg-Olofsson,[3] Mona Landin-Olsson,[7] Johan Jendle,[8] Soffia Gudbjörnsdóttir,[3,4] the Swedish National Diabetes Register

[1]Department of Endocrinology, Aarhus University Hospital, Aarhus Denmark

[2]Department of Public Health and Caring Sciences/Family and Preventive Medicine, Uppsala University, Uppsala, Sweden

[3]Institute of Medicine

ABSTRACT

OBJECTIVE
To investigate the long term effects of continuous subcutaneous insulin infusion (insulin pump therapy) on cardiovascular diseases and mortality in people with type 1 diabetes.

disease per 1000 person years; corresponding figures were 3.3 for fatal cardiovascular disease and 5.7 for all cause mortality. When lower body mass index and previous cardiovascular diseases were excluded, results of subgroup analyses

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- Isabelle Steineck
- Läkare
- Doktorand, Hvidovre Hospital

NDR NATIONELLA DIABETESREGISTRET

Hur påverkar insulinpump risken för att dö i hjärtkärlsjukdom?

Bakgrund

- Det är oklart om administrering av insulin med pump ökar eller minskar förekomsten av död i hjärtkärlsjukdom jämfört med att inte administrera insulin med pump.

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Observational study
Swedish National Diabetes Register (NDR)

- 18 168 personer med typ 1 diabetes i Sverige
- Epidemiologiska definition:
  enbart insulin + debut ålder <30 years
- 2 441 med insulinpump under hela studieperioden
- 15 727 med injektionsbehandling under hela studieperioden.

**Observational study of insulin pump treatment
Swedish National Diabetes Register (NDR)**

- Inklusionsperiod 2005-2007
- Följdes år 2005-2012
- Observationstiden var i medeltal 6,8 år

NDR ○ **NATIONELLA
DIABETESREGISTRET**

Baseline

	Pump	Injections	P value
	Crude, unadjusted data		
Numbers	2,441	15,727	-
Age (years)	38±13	41±15	<0.001
Diabetes duration (years)	25±12	26±15	<0.001
Males %	45.0	57.1	<0.001
HbA1c (mmol/mol)	63±12	64±14	0.4
Systolic BP (mmHg)	125±15	128±16	<0.001
Diastolic BP (mmHg)	73±8	73±9	0.1
Antihypertensive drugs %	31.8	36.0	<0.001
Total cholesterol (mmol/l)	4.7±0.8	4.8±0.9	<0.001
HDL cholesterol (mmol/l)	1.6±0.4	1.6±0.5	0.2
Triglycerides (mmol/l)	1.0±0.6	1.1±0.7	<0.001
Lipid drugs %	20.7	25.9	<0.001
BMI (kg/m^2)	25.3±3.8	25.5±4.1	0.1
Low physical activity %	16.1	19.9	<0.001
Creatinine (μmol/l)	81±46	85±55	0.003
GFR <60 %	9.7	11.2	0.02
Smokers %	9.9	12.8	<0.001
Cumulative Albuminuria %	19.8	23.1	<0.001
ASA %	14.6	18.4	<0.001
Previous CVD %	5.4	8.0	<0.001
Previous heart failure %	0.9	2.3	<0.001
Previous atrial fibrillation %	0.6	1.0	0.05
Previous cancer, %	0.9	1.2	0.2
Previous liver diseases, %	0.3	0.2	0.5
Previous mental disorders%	2.0	1.8	0.6
Education score 1-3	2.4±0.6	2.1±0.7	<0.001

Crude unadjusted data, P values with Student's t-test or X^2-test

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Crude unadjusted data, P values with Student's t-test or X^2-test

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18,168 patients with type 1 diabetes followed for 7 years, 2005-2012, baseline data

	Pump	Injections	P value	P value*
		Crude, unadjusted data		
Numbers	2,441	15,727	-	
Age (years)	38±13	41±15	<0.001	0.6
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Previous heart failure %	0.9	2.3	<0.001	0.4
Previous atrial fibrillation %	0.6	1.0	0.05	0.5
Previous cancer, %	0.9	1.2	0.2	0.8
Previous liver diseases, %	0.3	0.2	0.5	0.6
Previous mental disorders%	2.0	1.8	0.6	0.4
Education score 1-3	2.4±0.6	2.1±0.7	<0.001	0.15

P values* after adjustment with a propensity score including all variables in the table
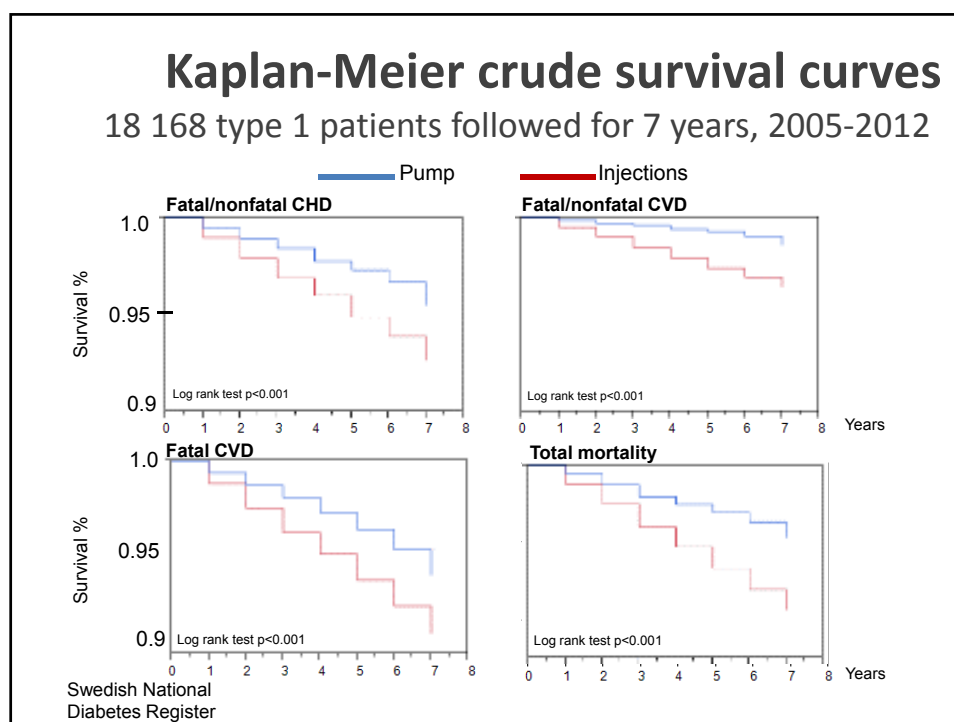
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Kaplan-Meier crude survival curves
18 168 type 1 patients followed for 7 years, 2005-2012

Pump — Injections

Fatal/nonfatal CHD

Survival %

Log rank test p<0.001

Fatal/nonfatal CVD

Log rank test p<0.001

Years

Fatal CVD

Survival %

Log rank test p<0.001

Total mortality

Log rank test p<0.001

Years

Swedish National
Diabetes Register

Table 2 Hazard ratio (95% confidence intervals) for various outcomes with insulin pump treatment compared with multiple daily injections (MDIs) in 18 168 people with type 1 diabetes followed for mean of 6.8 years from 2005 to 2012

|	No with events (%)	Events/1000 person years	Hazard ratio* (95% CI)	P value
Major endpoints				
Fatal/non-fatal coronary heart disease:				
MDIs	15 727/1058 (6.7)	10.7	1.0	0.05
Pump	2441/97 (4.0)	6.2	0.81 (0.66 to1.01)	
Fatal/non-fatal cardiovascular disease:				
MDIs	15 727/1294 (8.2)	13.1	1.0	0.2
Pump	2441/129 (5.3)	8.3	0.88 (0.73 to1.06)	
Fatal cardiovascular disease:				
MDIs	15 727/517 (3.3)	5.1	1.0	0.005
Pump	2441/29 (1.2)	1.8	0.58 (0.40 to 0.85)	
Total mortality:				
MDIs	15 727/1109 (7.1)	11.0	1.0	0.007
Pump	2441/83 (3.4)	5.3	0.73 (0.58 to 0.92)	
Secondary endpoints				
Fatal coronary heart disease:				
MDIs	15 727/453 (2.9)	4.5	1.0	0.004
Pump	2441/24 (1.0)	1.5	0.55 (0.36 to 0.83)	
Fatal stroke:				
MDIs	15 727/79 (0.5)	0.8	1.0	0.4
Pump	2441/5 (0.2)	0.3	0.67 (0.27 to 1.67)	
Non-cardiovascular disease mortality:				
MDIs	15 722/592 (3.8)	5.9	1.0	0.3
Pump	2441/54 (2.2)	3.4	0.86 (0.64 to 1.13)	

Principal findings

- Hos de 2 441 personer som behandlades med insulinpump, jämfört med de 15 727 personer som fick insulin med sprutor, var dödligheten i hjärtsjukdom 45 procent lägre, i hjärtkärlsjukdom 42 procent lägre och den totala dödligheten 27 procent lägre.
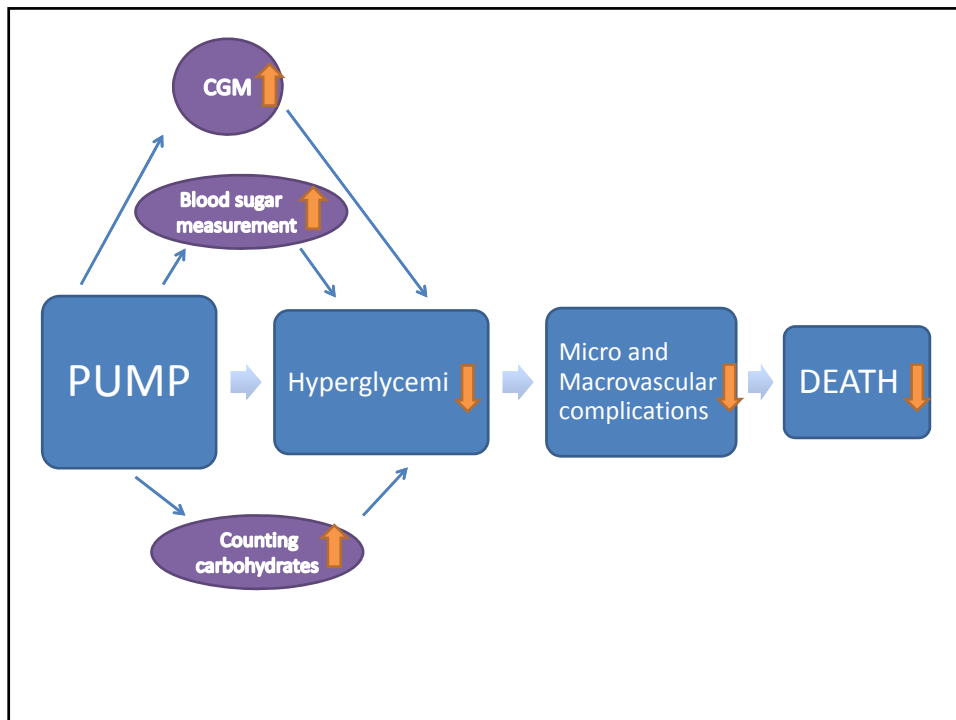
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Diskussion

- Varför ses denna samvariation?
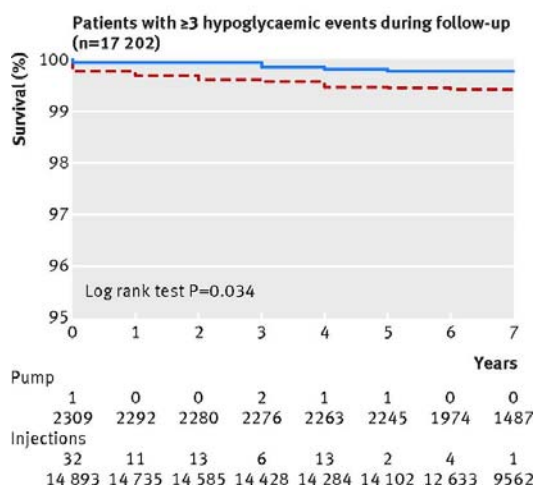
NDR NATIONELLA DIABETESREGISTRET
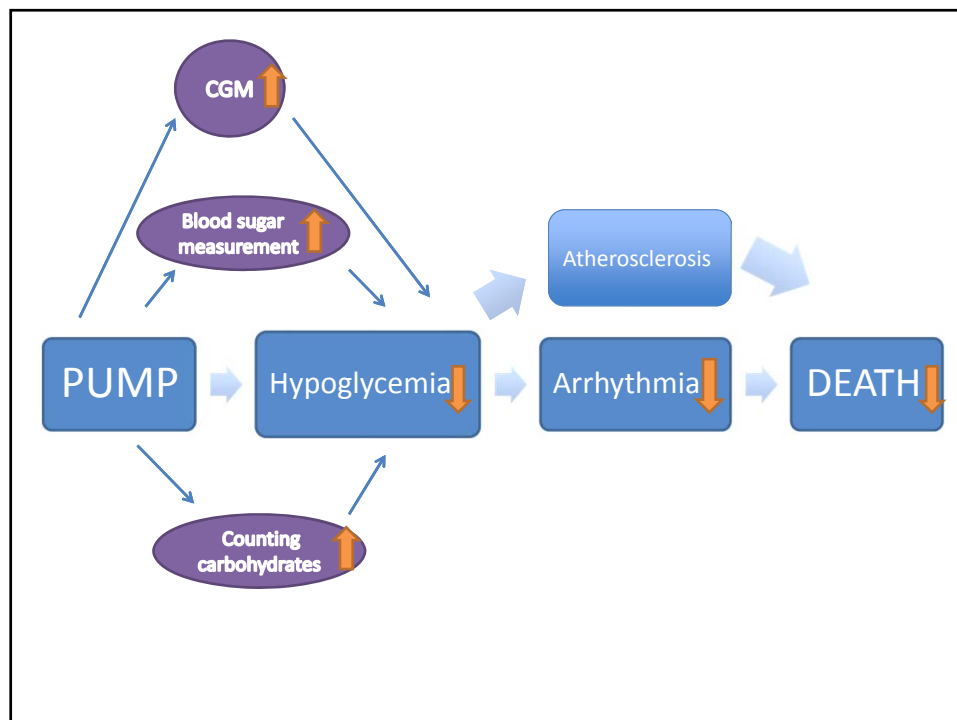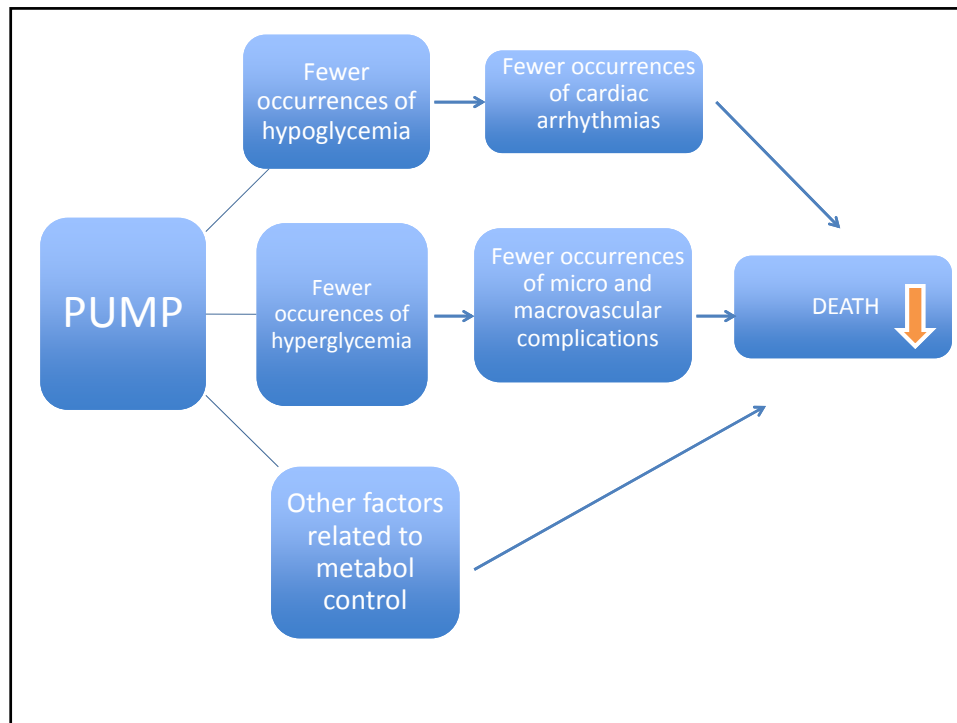
Analyses during study period

- Kaplan-Meier survival curves for first incident hypoglycaemic events in patients with type 1 diabetes during seven years of follow-up.

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Kaplan-Meier analysis disclosed significantly fewer (P=0.034) hypoglycaemic incidents with insulin pump therapy compared with multiple daily injections in patients with three or more incidents during seven years of follow-up

Patients with ≥3 hypoglycaemic events during follow-up (n=17 202)

Log rank test P=0.034

Pump							
1	0	0	2	1	1	0	0
2309	2292	2280	2276	2263	2245	1974	1487

Injections

| 32	11	13	6	13	2	4	1
14 893	14 735	14 585	14 428	14 284	14 102	12 633	9562

Konklusion

- I denna observationella studie av individer med typ 1 diabetes innebar behandling med insulinpump, istället för med sprutor, en reducerad dödlighet i hjärtsjukdom, hjärtkärlsjukdom och dödlighet totalt sett.

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Conclusions

- Whether the results reflect the physiological consequences of insulin pump treatment, the clinical management that pump users receive, or the educational aspects of having the pump remains elusive
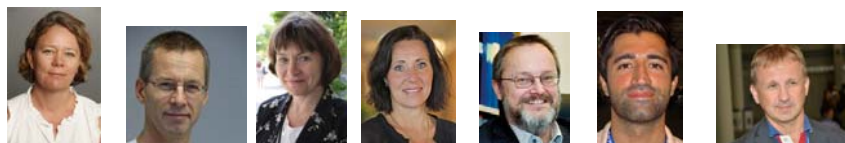
Effect of an unknown factors

Fatal CVD:
An unknown binary covariat with HR 1.3 must be present in at least 60% more patients with injections than in patients with pump treatment to invalidate the significance.

Total mortality:
An unknown binary covariat with HR 1.3 must be present in at least 40% more patients with injections than in patients with pump treatment to invalidate the significance.

			Confounder with hazard ratio 1.3	
			P (confounder) * for insulin pump	
			0.0	0.2
Fatal CVD	P (confounder) *	0.0	0.59 (0.40-0.86)	0.56 (0.38-0.81)
	for injections	0.2	0.63 (0.42-0.91)	0.59 (0.40-0.86)
		0.4	0.66 (0.45-0.96)	0.63 (0.42-0.91)
		0.6	**0.70 (0.47-1.01)**	0.66 (0.45-0.96)
		0.8	**0.73 (0.50-1.07)**	**0.70 (0.47-1.01)**
Total mortality	P (confounder) *	0.0	0.75 (0.59-0.93)	0.71 (0.56-0.88)
	for injections	0.2	0.80 (0.63-0.98)	0.75 (0.59-0.93)
		0.4	**0.84 (0.66-1.04)**	0.80 (0.63-0.98)
		0.6	**0.89 (0.70-1.10)**	**0.84 (0.66-1.04)**
		0.8	**0.93 (0.73-1.15)**	**0.89 (0.70-1.10)**

* P (confounder) is the prevalence of the confounder being present. **Bold red** = non-significant hazard ratios.