Region Västra Götaland, HTA-centrum

Regional activity-based HTA [Verksamhetsbaserad HTA]

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Efficacy and safety of advanced hybrid closed loop systems compared with multiple daily injections or open loop systems, in adults with type 1 diabetes

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Efficacy and safety of advanced hybrid closed loop insulin pump systems compared with multiple daily injections or open loop systems, in adults with type 1 diabetes

[Effekt och säkerhet hos avancerade hybridsystem med insulinpump och sluten återkopplingskrets, jämfört med pennbehandling med insulin och sensor eller med insulinpumpsystem utan återkopplingskrets, hos vuxna med typ 1-diabetes]

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1. Abstract

Background

Type 1 diabetes is a severe chronic disease with ceased insulin production and risk of both acute and long-term complications and shorter life expectancy compared with the general population. There are several different insulin replacement therapies for diabetes, such as multiple daily injections (MDI) with insulin combined with continuous glucose monitoring in interstitial fluid (sensor), or insulin pump with integrated or separate sensor based continuous glucose monitoring (sensor augmented pump, SAP). In recent years, a new insulin pump with integrated sensor technology has become available on the market, a so-called advanced hybrid closed loop (AHCL) system where sensor data automatically lead to pump adjustments but also leave room for manual adjustments.

Question at issue

Does the use of an AHCL system, compared with either MDI with sensor or with SAP, improve blood glucose control and quality of life and reduce the risk for diabetes complications in adults with type 1 diabetes, and without compromising safety?

Methods

During May 2022, with an update in December 2022, two authors performed systematic searches in three databases, and by assessing abstract and full-text articles made a first selection of full-text articles for inclusion or exclusion. At least two authors independently read and decided in consensus which articles should be included. Those articles were then critically appraised. Data was extracted by one author and checked by another and were pooled in meta-analysis if possible. The GRADE system was used for assessment of certainty of evidence.

Results

Ten randomised controlled trials (RCT) (six with parallel design, four with cross-over design) (n=667) and five non-randomised studies (n=141) were included. In general, the studies suffered from some indirectness, some to very serious study limitations, and from uncertain precision to very serious imprecision. For the comparison AHCL vs MDI+ intermittent scanning sensor, we found only one RCT (n=82) which was based on a high-risk population with increased haemoglobin A1c (HbA1c) at baseline that was followed for 6 months. For the comparison AHCL vs SAP with or without predictive low glucose suspend, we found nine RCTs (n=585) based on a normal risk population with lower HbA1c values.

Results for AHCL vs MDI+sensor:

The single identified study was based on a high-risk adult population with substantially elevated HbA1c

Mortality and angiopathy: No data was found.

Emergency events (severe hypoglycaemia, ketoacidosis): It is uncertain whether there is any difference in emergency events (not assessed according to GRADE).

Haemoglobin A1c (HbA1c) (an overall measure of glycaemic control): Use of ACHL may result in a clinically relevant reduction in HbA1c (GRADE ⊕⊕◯◯).

Health-related quality of life (HQoL): It is uncertain whether there is any difference in HQoL (GRADE ⊕◯◯◯).

Time in range (TIR) 3.9-10.0 mmol/L, % (a measure of time spent in optimal glycaemic control): AHCL may result in an increased TIR (GRADE ⊕⊕◯◯).

Time below range (TBR) (<3.9 mmol/L, hypoglycaemia), %: There may be little or no difference in TBR (GRADE ⊕⊕◯◯).

Time above range (TAR) (>10.0 mmol/L, hyperglycaemia), %: Use of AHCL may result in a decreased TAR (GRADE ⊕⊕◯◯).

Glucose variability %: There may be little or no difference in glucose variability (GRADE ⊕⊕◯◯).

Patient reported outcomes: There may be an improvement in diabetes treatment satisfaction and a decrease in fear of hypoglycaemia with AHCL (GRADE ⊕⊕◯◯).

Adverse events (except severe hypoglycaemia and ketoacidosis): Use of AHCL may result in an increased number of mainly technology-related non-serious adverse events (GRADE ⊕⊕◯◯).

Results for AHCL vs SAP in a mixed risk adult population:

Mortality and angiopathy: No data was found.

Emergency events (severe hypoglycaemia, ketoacidosis): It is uncertain whether there is any difference in emergency events (GRADE ⊕◯◯◯).

Haemoglobin A1c (HbA1c) (an overall measure of glycaemic control): It is uncertain whether there is any difference in HbA1c (GRADE ⊕◯◯◯).

Health-related quality of life (HQoL): No data was found.

Time in range (TIR) 3.9-10.0 mmol/L, % (a measure of time spent in optimal glycaemic control): Use of AHCL probably results in an increased TIR (GRADE ⊕⊕⊕◯).

Time below range (TBR) (<3.9 mmol/L, hypoglycaemia), %: Use of AHCL probably results in a reduction of time below range (GRADE ⊕⊕⊕◯).

Time above range (TAR) (>10.0 mmol/L, hyperglycaemia), %: Use of AHCL probably results in a decreased TAR (GRADE ⊕⊕⊕◯).

Glucose variability, %: Use of AHCL may result in a reduction of glucose variability (GRADE ⊕⊕◯◯).

Patient reported outcomes: It is uncertain whether there is any difference in patient reported outcomes (GRADE ⊕◯◯◯).

Adverse events (except severe hypoglycaemia and ketoacidosis): It is uncertain whether there is any difference in adverse events (GRADE ⊕◯◯◯).

Economical aspects

The cost of an AHCL system is approximately 69-77,000 SEK (average per year over first 4 years per patient) and for SAP systems approximately 65-73,000 SEK (average per year over first 4 years per patient). The corresponding costs with MDI+sensor is approximately 26-47,000 SEK (average per year over first 4 years per patient). Currently, about 70% of type 1 diabetes patients use multiple injections + sensor and a switch to AHCL systems will generate substantially increased costs in the health care system.

Ethics

The ethical dilemma consists in weighing a likely but undocumented future reduction in diabetic complications against an immediate and very substantial displacement effect that will be generated by rapid transfer of a large number of patients from sensor in combination with multiple daily pen injections to AHCL systems. According to the ethical Medical Need principle, one should in this situation give priority to patients not sufficiently well controlled by use of sensor in combination with multiple daily pen injections.

Conclusion

This HTA report shows that in a **high-risk population**, as reflected by increased baseline HbA1c, AHCL may result in a large increase in TIR and a slight decrease in TAR. It may also result in clinically relevant reductions of HbA1c compared with baseline, when compared with MDI with sensor. In a **normal-risk** population, AHCL probably improves the sensor-related glycaemic outcomes TIR, TBR and TAR when compared with SAP, but had no consistent effect on HbA1c and it was uncertain whether AHCL improves patient satisfaction measured with validated instruments. A major shortcoming of the documentation is that the effects on long-term complications of the consistent but numerically moderate changes in the glycaemic variables is unknown.

2. Populärvetenskaplig sammanfattning – Plain language summary in Swedish

Typ 1 diabetes är en allvarlig kronisk sjukdom där insulinproduktionen har upphört. Risken för både akuta och kroniska komplikationer ökar och om sjukdomen inte sköts ordentligt kan livslängden förkortas jämfört med befolkningen i stort. Det finns flera olika behandlingsformer där den vanligaste är egna injektioner med en insulinpenna i kombination med en glukosmätare som sitter under huden och kontinuerligt mäter glukosnivån i vävnadsvätskan. Huvudalternativet är att tillföra insulin med hjälp av en liten pump som kontinuerligt tillför varierande mängder insulin i underhudsfettet. Patienten får själv dosera insulin baserat på glukosvärdena från avkännaren. Den tredje och senaste varianten i utvecklingen är så kallade avancerade hybridpumpsystem, där pumpen i huvudsak automatiskt styrs av glukoshalten i vävnaden, med hjälp av en digital återkopplingskrets. Patienten måste dock fortfarande själv i vissa situationer styra pumpen, tex i samband med måltider.

I denna rapport har vi utvärderat frågeställningen huruvida avancerade hybridpumpsystem är överlägsna alternativen pennbehandling med insulin och sensor, respektive egenstyrd insulinpump med tillhörande sensor.

Metod

Under maj 2022, med en uppdatering i december 2022, gjorde två författare systematiska litteratursökningar. Minst två författare läste och beslutade i samförstånd vilka artiklar som skulle ingå, och kvalitetsgranskade dessa. Efter dataextraktion bedömdes det vetenskapliga underlagets tillförlitlighet.

Resultat

Totalt 15 studier med 808 vuxna personer med typ 1 diabetes inkluderades i denna rapport. Studierna hade vissa begränsningar i form av generaliserbarhet, vissa eller allvarliga andra studiebegränsningar samt osäkerhet eller allvarliga brister i precision. Vi identifierade inga studier med utfallen dödlighet eller långtidskomplikationer.

Avancerade hybridpumpsystem jämfört med pennbehandling med sensor i en vuxen population med initialt högt HbA1c och därmed ökad risk för diabetes-komplikationer:

- *Dödlighet och kärlkomplikationer:* Inga data.
- *Akuta händelser:* Det är osäkert om det finns någon skillnad i akuta händelser.
- *Hemoglobin A1c (HbA1c) (mått på den övergripande blodsockerkontrollen): D*et är möjligt att ett avancerat hybridpumpsystem kan leda till en minskning av HbA1c.
- *Hälsorelaterad livskvalitet:* Det är osäkert om det finns någon skillnad i livskvalitet.
- *Tid i målintervallet 3.9–10.0 mmol/L (mått på tid i optimal blodsockerkontroll):* Ett avancerat hybridpumpsystem kan leda till en ökad tid inom målområdet 3.9–10.0 mmol/L.

- *Tid <3.9 mmol/L (hypoglykemi/ för lågt blodsocker):* Det är möjligt att det inte finns någon skillnad i tid i intervallet under 3.9 mmol/L.
- *Tid >10.0 mmol/L (hyperglykemi/ för högt blodsocker):* Ett avancerat hybridpumpsystem kan leda till en minskad tid i intervallet över 10.0 mmol/L.
- *Glukossvängningar:* Det är möjligt att det inte finns någon skillnad i glukossvängningar.
- *Patientrapporterade mått:* Det kan finnas en ökad nöjdhet med tekniken och en minskning av rädslan för hypoglykemi med en avancerad hybridpump.
- *Biverkningar/negativa händelser:* Det kan finnas ett ökat antal negativa händelser av låg allvarlighetsgrad med ett avancerat hybridpumpsystem.

Avancerade hybridpumpsystem jämfört med egenstyrd insulinpump med tillhörande sensor i en vuxen population med normalt eller lätt förhöjt HbA1c (dvs med lägre risk för diabetes-komplikationer än gruppen ovan):

- *Dödlighet och kärlkomplikationer:* Inga data.
- *Akuthändelser:* Det är osäkert om det finns någon skillnad i akuta händelser.
- *Hemoglobin A1c (HbA1c) (mått på den övergripande blodsockerkontrollen):* Det är osäkert om det finns någon skillnad i HbA1c.
- *Hälsorelaterad livskvalitet:* Inga data.
- *Tid i målintervallet 3.9–10.0 mmol/L (mått på tid i optimal blodscokerkontroll):* Ett avancerat hybridpumpsystem leder troligen till en ökad tid inom intervallet 3.9–10.0 mmol/L.
- *Tid <3.9 mmol/L (hypoglykemi/ för lågt blodsocker):* Ett avancerat hybridpumpsystem leder troligen till en minskad tid i intervallet <3.9 mmol/L.
- *Tid >10.0 mmol/L (hyperglykemi/ för högt blodsocker):* Ett avancerat hybridpumpsystem leder troligen till en minskad tid i intervallet >10.0 mmol/L.
- *Glukossvängningar:* Ett avancerat hybridpumpsystem kan leda till minskade glukossvängningar.
- *Patientrapporterade mått:* Det är osäkert om det finns någon skillnad i patientrapporterade resultat.
- *Biverkningar/negativa händelser:* Det är osäkert om det finns någon skillnad i kliniskt relevanta negativa händelser.

Kostnader

Kostnaden för ett avancerat hybridpumpsystem beräknas till cirka 69–77,000 SEK (genomsnitt per år under de första 4 åren per patient. Egenstyrd insulinpump med tillhörande sensor beräknas kosta cirka 65–73,000 SEK (genomsnitt per år under de första 4 åren per patient. Pennbehandling med sensor beräknas kosta ca 26–47,000 SEK (genomsnitt per år under de första 4 åren per patient. Idag använder i storleksordningen 70% av patienterna med typ 1-diabetes pennbehandling och en generell övergång till hybridsystem kommer att medföra mycket betydande merkostnader för sjukvården.

Etiska aspekter

Det saknas data vad gäller kopplingen mellan de sensormätta utfallen (tex TIR) och långtids-komplikationer. Ett generellt införande av de nya systemen kommer med hög sannolikhet att medföra betydande bortträngningseffekter. Kostnadseffektiviteten vad gäller eventuellt förhindrande av kliniska utfall får anses okänd. Det etiska dilemmat blir därför hur man skall väga dessa två: en hög men vetenskapligt odokumenterad sannolikhet för gynnsamma kliniska effekter jämfört meden hög risk för omedelbara och betydande bortträngningseffekter som konsekvens av övergång från pennbehandling till hybridsystem.

Enligt den etiska Behovsprincipen bör en sådan övergång i första hand erbjudas patienter som inte är välkontrollerade med penninjektioner med insulin och dosering baserad på sensordata.

Slutsatser

Avancerade hybridpumpsystem verkar möjliggöra en ytterligare stabilisering av vävnadsglukosnivåerna utöver den som uppnås med manuell styrning eller pennbehandling. Underlaget är emellertid litet och av varierande kvalitet Vi identifierade ingen ökad risk för allvarliga komplikationer. Gällande andra mindre avvikelser rapporteras dessa oftare bland användare av ett avancerat hybridpumpsystem. Försöken att utvärdera patientnöjdhet antyder att denna kan vara något förbättrad jämfört med pennbehandling i en population med initialt sämre glukoskontroll och väsentligen likvärdig jämfört med manuell pumpkontroll. Den viktigaste bristen i dokumentationen är att det hittills finns mycket begränsade data vad gäller sambandet mellan de nya kontinuerliga måtten på glukoskontroll och risk för långtidskomplikationer av diabetessjukdomen.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the regional board for quality assurance of activity based HTA. The abstract is a concise summary of the results of the systematic review. The plain language summary in Swedish is intended for decision makers.

Christina Bergh, Professor, MD

Head of HTA-centrum, Region Västra Götaland, Sweden, April 26th 2023.

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DDS Doctor of dental surgery

MD Medical doctor

PhD Doctor of Philosophy

OD Odontology doctor

PT Physiotherapist

RN Registered Nurse

3. Summary of findings

C1: Advanced hybrid closed loop system vs insulin administration via multiple daily injections with intermittent scanning continuous glucose monitoring (sensor). Results based on an adult population with uncontrolled HbA1c.

Outcomes	No. of studies, design (n, patients)	Absolute effect (95% CI) AHCL Mean (SD) unless otherwise stated	Absolute effect (95% CI) MDI+sensor Mean (SD) unless otherwise stated	Difference between groups Mean (SD) unless otherwise stated	Certainty of evidence GRADE*
Mortality	No studies				
Angiopathy (macro- or micro-)	No studies				
Emergency events (severe hypo-glycaemia, ketoacidosis)	1 RCT, parallel design (n=82)	No events	No events		No GRADE[1]
HbA1c*	1 RCT, parallel design (n=82)	AHCL: 7.32 (0.61) %	MDI+sensor: 8.91 (0.78) %	-1.42 (-1.74 to -1.10) % p<0.0001	⊕⊕◯◯[2] Favours AHCL
Health-related quality of life DQoL total score**	1 RCT, parallel design (n=82)	Change from baseline: 5.9 (10.60)	Change from baseline: 1.5 (10.08)	3.8 (-2.1 to 9.7) p=0.20	⊕◯◯◯[3] No difference
Time in range*** 3.9–10 mmol/L	1 RCT, parallel design (n=82)	70.6 (9.70) %	43.6 (15.37) %	27.6 (21.63 to 33.6) % p<0.0001	⊕⊕◯◯[2] Favours AHCL
Time below range <3.9 mmol/L	1 RCT, parallel design n=82	2.6 (2.01) %	2.6 (2.55) %	0.1 (-0.7 to 1.0) % n.s.	⊕⊕◯◯[2] No difference
Time above range >10 mmol/L	1 RCT, parallel design (n=82)	26.7 (10.44) %	53.8 (16.47) %	-27.9 (-34.2 to -21.6) % p<0.0001	⊕⊕◯◯[2] Favours AHCL
Glucose variability****	1 RCT, parallel design (n=82)	35.5 (4.46) %	35.9 (5.74) %	0.6 (-1.4 to 2.5) % n.s.	⊕⊕◯◯[2] No difference
Patient reported outcomes***** DTSQs DTSQc HFS-II	1 RCT, parallel design (n=82)	Change from baseline: 6.1 (7.55) 13.7 (4.39) -10.2 (15.51)	Change from baseline: 0.2 (6.84) 3.7 (7.24) -2.7 (13.08)	6.2 (2.9 to 9.4) p=0.0003 9.8 (7.04 to 12.64) p<0.0001 -6.9 (-13.5 to -0.3) p<0.041	⊕⊕◯◯[4] Favours AHCL

Adverse events	1 RCT, parallel design (n=82)	AHCL: 1 serious event 56 device deficiencies 66 non-serious adverse events For details see Appendix 4.9	Manual insulin injections: 1 serious event 1 diabetes-related hospitalization 1 emergency room admission 8 device deficiencies 39 non-serious events For details see Appendix 4.9	NA	⊕⊕◯◯[2] Favours MDI+sensor

* Minimal important difference (MID)=0.5%, **DQoL total score 0-100 (higher scores positive), ***Minimal important difference (MID)= 5%, ****Target ≤36%, *****DTSQs score 0 to 36 and DTSQc score -18 to 18 (higher scores positive), HFS-II score 0-132 (higher score indicates increased fear)

AHCL: advanced hybrid closed loop, C: control, CI: confidence interval, DQoL: Diabetes Quality of Life, DTSQc: Diabetes Treatment Satisfaction Questionnaire change, DTSQs: Diabetes Treatment Satisfaction Questionnaire status, HbA1c: haemoglobin A1c, HFS-II: Hypoglycaemia Fear Survey, n.s.: non-significant, NA: not applicable, RCT: randomised controlled trial

Reasons for downgrading (stated for the RCTs only, since they were pivotal for the GRADE assessment):

[1]Due to no events.

[2]Serious study limitations (large involvement of industry, unclear ITT analysis, uncertain precision

[3]Very serious study limitations (large dropout and involvement of industry, not blinded, subjective, unclear intention to treat (ITT) analysis), serious imprecision

[4]Serious study limitations (large involvement of industry, not blinded, subjective, unclear ITT analysis), serious imprecision

C2: Advanced hybrid closed loop system vs insulin administration via insulin pump with integrated or separate sensor based continuous glucose monitoring and with or without predictive low glucose suspend. Results based on a mixed risk population

Outcomes	No. of studies, design (n, patients)	Absolute effect (95% CI) AHCL	Absolute effect (95% CI) SAP	Difference between groups Mean (SD) unless otherwise stated	Certainty of evidence GRADE*
Mortality	No studies				
Angiopathy (macro- or micro-)	No studies				
Emergency events	2 RCT's, parallel design (n=47+15) 3 RCTs, cross-over design (n=68+26+93) 3 non-randomised studies (n=62)	Severe hypoglycaemia: 6 events, p=0.252 Diabetic ketoacidosis: 0 events No events	Severe hypoglycaemia: 5 events Diabetic ketoacidosis: 0 events No events	NA	⊕◯◯◯[1] No difference
HbA1c*	1 RCT, parallel design (n=15) 1 RCT, cross-over design (n=68) 3, non-randomised studies (before-after) (n=55)	7.32 (0.55) %, n.s. Change from baseline: -0.29 (0.6) %	7.18 (1.30) % Change from baseline: -0.14 (0.6) %	Mean difference: 0.14 (-0.96 to 1.24) -0.15 (-0.33 to 0.03) % p=0.098 Difference: -0.34 (-0.55 to -0.13) p=0.001	⊕◯◯◯[2] No difference
Health-related quality of life	No data				
Time in range** 3.9-10 mmol/L	3 RCTs, parallel design (2 with secondary analysis) (n= 208) 2 RCTs, cross-over design (n=140) 3 non-randomised (before-after) (n=81)	Varies from 63.0 to 78.2% Varies from 73.0 to 79.6%	Varies from 55.0 to 66.0% Varies from 62.0 to 69.6%	10.54 (8.01 to 13.07) %, p=0.00001 Difference: 9.79 (7.05-12.52), p<0.00001	⊕⊕⊕◯[3] Favours AHCL
Time below range < 3.9 mmol/L	3 RCTs, parallel design (n=139) 2 RCTs, cross-over design (n=169) 2 non-randomised (before/ after) (n=46)	Varies from 1.6 to 2.8% Varies from 0.8 to 1.5%	Varies from 2.5 to 4.8% Varies from 1.2 to 1.7%	-1.80 (-2.56 to -1.04%), p<0.00001) Difference: -0.24 (-0.86 to 0.37), n.s.	⊕⊕⊕◯[4] Favours AHCL

Time above range > 10 mmol/l	3 RCTs parallel design (n=139) 2 RCTs, cross-over design (n=209) 3 non-randomised studies (before/ after) (n=83)	Varies from 19.8 to 35.0% Varies from 19.3 to 24.4%	Varies from 35.6 to 43.0% Varies from 26.6 to 35.6%	-7.91 (-10.32 to -5.49) %, p< 0.00001 -10.10 (-13.31 to -6.90), p<0.00001	⊕⊕⊕◯[3] Favours AHCL
Glucose variability*** (Coefficient of variation = 100*SD glucose/mean glucose)	1 RCT, parallel design (n=15) 2 RCTs, cross-over design (n=140) 4 non-randomised studies (before/ after) (n=112)	Varies from 31.0 to 35.0% Varies from 29.0 to 34.0%	Varies from 33.3 to 37.8% Varies from 33.3 to 38.0%	-2.88 (-3.82 to -1.94%), p<0.00001 -3.28 (-4.62 to -1.94) p<0.00001	⊕⊕◯◯[5] Favours AHCL
Patient reported outcomes****	1 RCT, parallel design, (n=120) 2 RCTs, cross-over design (n=97) 2 non-randomised studies (n=49)	1 RCT (cross-over): VAS difficulty to use: 6.9 (2.8) 1 RTC (cross-over): DTSQs: 30.9 (0.7) DTSQc: 11.7 (0.8) Remaining outcomes were n.s See Appendix 4.8 for data	1 RCT (cross-over): VAS difficulty to use: 8.0 (1.8) 1 RTC (cross-over): DTSQs: 27.9 (0.7) DTSQc: 9.2 (0.9) See Appendix 4.8 for data	-1.10 (-1.92 to -0.28) p=0.004 p=0.032	⊕◯◯◯[6] No difference
Adverse events	1 RCT, parallel design (n=47) 2 RCTs, cross-over design (n=161) 3 non-randomised studies (n=62)	See Appendix 4.9 for data	See Appendix 4.9 for data	NA	⊕◯◯◯[7] No difference

* Minimal important difference (MID) for the % units used in the publications=0.5%, ** MID=5%, ***target ≤36%, **** DTSQs score 0 to 36 and DTSQc score -18 to 18 (higher scores positive), VAS score 0-10 (higher scores are positive)

AHCL: advanced hybrid closed loop, C: control, CI: confidence interval, DTSQ: Diabetes Treatment Satisfaction Questionnaire, DTSQc: Diabetes Treatment Satisfaction Questionnaire change, DTSQs: Diabetes Treatment Satisfaction Questionnaire status, HbA1c: haemoglobin A1c, HFS-II: Hypoglycaemia Fear Survey, IQR: interquartile range, NA: not applicable, n.s.: non-significant, PLGS: predictive low glucose suspend, RCT: randomised controlled trial, SAP: sensor augmented pump, SD: standard deviation, VAS: Visual Analogical Scales

Reasons for downgrading (stated for the RCTs only, since they were pivotal for the GRADE assessment):

[1]Some indirectness (limited adult info, moderate to high-risk population), serious study limitation (unblinded, potential industry involvement, unclear randomisation, secondary observation), very serious imprecision

[2]Some indirectness (mixed-age population, limited adult info), some study limitations (unblinded, potential industry involvement, insufficient info and statistics), serious inconsistency and imprecision

[3] Some indirectness (mixed-age population, limited adult info, unclear recruitment), some study limitations (unblinded, potential industry involvement, unclear randomisation)

[4] Some indirectness (mixed-age population, limited adult info, unclear recruitment), some study limitations (unblinded, potential industry involvement, unclear randomisation), uncertain precision

[5] Some indirectness (mixed-age population, limited adult info, unclear recruitment), some study limitations (unblinded, potential industry involvement, unclear randomisation), some inconsistency, serious imprecision

[6] Some indirectness (limited adult info), serious study limitation (unblinded, potential industry involvement, subjective outcomes, unclear randomisation), some inconsistency, serious imprecision

[7] Some indirectness (moderate to high-risk population, one group more men), serious study limitation (unblinded, potential industry involvement, unclear randomisation, secondary observation), very serious imprecision

***** Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

AHCL advanced hybrid closed loop

CI confidence interval

DCCT The Diabetes Control and Complications Trial

GRADE Grading of Recommendations, Assessment, Development and Evaluations

HbA1c haemoglobin A1c

HTA health technology assessment

isCGM: intermittently scanned continuous glucose monitoring

MDI multiple daily injections

mmol/L millimole per litre

NDR the Swedish National Diabetes Register

PICO Patients, Intervention, Comparison, Outcome

QALY quality-adjusted life years

RCT randomised controlled trial

SAP sensor augmented pump

SD standard deviation

SEK Swedish krona

TAR time above range

TBR time below range

TIR time in range

WHO World Health Organisation

5. Background

Disease/disorder of interest and its degree of severity

Type 1 diabetes is a chronic disease characterized by hyperglycaemia and a high risk of both acute and long-term complications. It is an autoimmune disease leading to the destruction of the insulin-producing beta cells in the pancreas causing insulin deficiency. Type 1 diabetes is a serious condition with impaired long-term survival compared to matched controls in the general population (Hallström et al., 2022, Rawshani et al., 2017a). Insulin replacement therapy is today the only option for treating hyperglycaemia in type 1 diabetes. Haemoglobin A1c (HbA1c) is a measure of glycaemic control that gives a picture of average blood glucose levels over approximately the last 3 months. There is a well-established link between HbA1c levels and the risk of subsequent development of chronic diabetes complications (The Diabetes Control and Complications Trial (DCCT), 1993, Nathan et al., 2005). Patients with poor glycaemic control eventually risk kidney failure, visual impairment, cardiovascular events, amputations, and premature death (DCCT, 1993, Nathan et al., 2005, Lind et al., 2014). Insulin treatment together with treatment of other cardiovascular risk factors and screening for microvascular disease are well established cornerstones in preventing diabetes complications (DCCT, 1993, Nathan et al., 2005, Rawshani et al., 2017b).

Insulin treatment in type 1 diabetes, with multiple daily injections (MDI) or with insulin pump therapy, is demanding for the person with diabetes and requires knowledge, self-management skills and confidence. The person with type 1 diabetes needs to balance food composition and intake, physical activity and emotional stress with glucose monitoring values and trends, as well as insulin timing and dose. The self-management is challenging and can be burdensome and diabetes-specific emotional stress is common in type 1 diabetes (Fisher et al., 2015).

In an international consensus document on management of type 1 diabetes, the overall goal of diabetes care is to support people with type 1 diabetes to live a long and healthy life. The aim is to have a blood glucose level as close to the normal range as possible and to avoid both hyper- and hypoglycaemia and prevent ketoacidosis. Another important goal for diabetes care is to provide approaches, treatments and devices that promote psychosocial well-being and minimise the psychosocial burden of living with type 1 diabetes and diabetes distress (Holt et al., 2021).

Self-monitoring of blood glucose and HbA1c have for more than three decades been the key measures of glycaemic control in diabetes. Since 2015 increased use of continuous glucose monitoring with subcutaneous sensors has resulted in new possibilities to assess glycaemic control. In Sweden continuous glucose monitoring is now standard in glucose monitoring in type 1 diabetes and has replaced most capillary glucose measurements. New sensor derived glucose metrics such as time in range (TIR), time below range (TBR) and measures of glucose variability (Coefficient of variation) are now established and interpreted according to international consensus-based target levels (Battelino et al., 2019).

Evidence that links TIR to diabetes complications in both type 1 and type 2 diabetes is evolving (Bellido et al., 2021, Advani, 2020, Raj et al., 2022). However, studies measure TIR in different ways, e.g. derived from 7-8 -point capillary glucose measurements or from 3-6 days of continuous glucose monitoring (sensor). Studies are often cross sectional and when longitudinal not powered to evaluate the predictive value of TIR separately from HbA1c. Nevertheless, in type 1 diabetes and with capillary glucose measurements from The Diabetes Control and Complications Trial (i.e. intermittent sampling, not continuous monitoring) it was shown that a decrease in TIR of 10%-units was associated with an increased risk of retinopathy by 64% (aHR= 1.64 (95% CI 1.51–1.78), p<0,001) and the risk of albuminuria by 40% (aHR = 1.40 (95% CI 1.25–1.56)), p<0,001) (Beck et al., 2019). The strongest association was seen at TIR values below 50%-units. In a Danish

longitudinal study on type 1 diabetes with sensor augmented insulin pump (mean change in TIR 13%), a 10%-unit increase in sensor derived TIR was associated with a reduction in the risk of albuminuria by 20% (Ranjan et al., 2020).
A study from Belgium on persons with type 1 diabetes using sensors over 24 months demonstrated that a lower TIR was associated with the presence of microvascular complications and hospitalisation for hypoglycaemia and ketoacidosis (El Malahi et al., 2022). Furthermore, using paired data from 18 studies a linear relationship between HbA1c and %-units TIR was seen with a 10% unit change in TIR being associated with a 9 mmol/mol change in HbA1c (Vigersky and McMahon, 2019).

Prevalence and incidence

According to the Swedish National Diabetes Register's (NDR) annual report 2021 there are 48,000 adults with type 1 diabetes in Sweden, with a mean age of 48 years and mean diabetes duration of 24 years. The type 1 diabetes group accounts for approximately 10% of persons with diabetes in Sweden. There are 8000 children with type 1 diabetes and for children in Sweden the incidence rate for type 1 diabetes was approximately 40 per 100,000 in 2020 and seems to be increasing. In Region Västra Götaland there are currently approximately 9000 adults and 1000 children with type 1 diabetes (NDR, 2022). Approximately 14 % of adults with type 1 diabetes in Sweden have a HbA1c >70 mmol/mol, i.e. are considered poorly regulated (NDR, 2022).

Present treatment

The most common insulin replacement regimen in adults with type 1 diabetes is still MDI of insulin, given subcutaneously. Modern insulin analogues are used with a combination of long-acting basal insulin, injected once or twice daily, and rapid-acting insulins taken at mealtime and for corrections of glucose excursions between meals, thus trying to mimic the physiologic need of insulin as closely as possible.

Insulin pumps have been on the market since the 1980s and have been an alternative way to administer insulin in patients whose needs are not being met with MDI-based treatment. Rapid-acting insulin is delivered as a continuous subcutaneous infusion covering basal insulin need and is combined with additional manual mealtime boluses. At high glucose values correction bolus doses can nowadays be administered manually or automatically depending on the insulin pump system. Both MDI and pump regimens can be used together with continuous glucose monitoring systems, which has been shown to improve glucose control further (Lind et al., 2017, Šoupal et al., 2020). According to the Swedish National Diabetes Register (2022), 92% of adults with type 1 diabetes have access to a sensor with intermittent scanning or real time continuous glucose monitoring in order to enhance the possibility to reach glucose levels as close to the normal range as possible without risking hypoglycaemic events.

Normal pathway through the healthcare system and current wait time for medical assessment/treatment

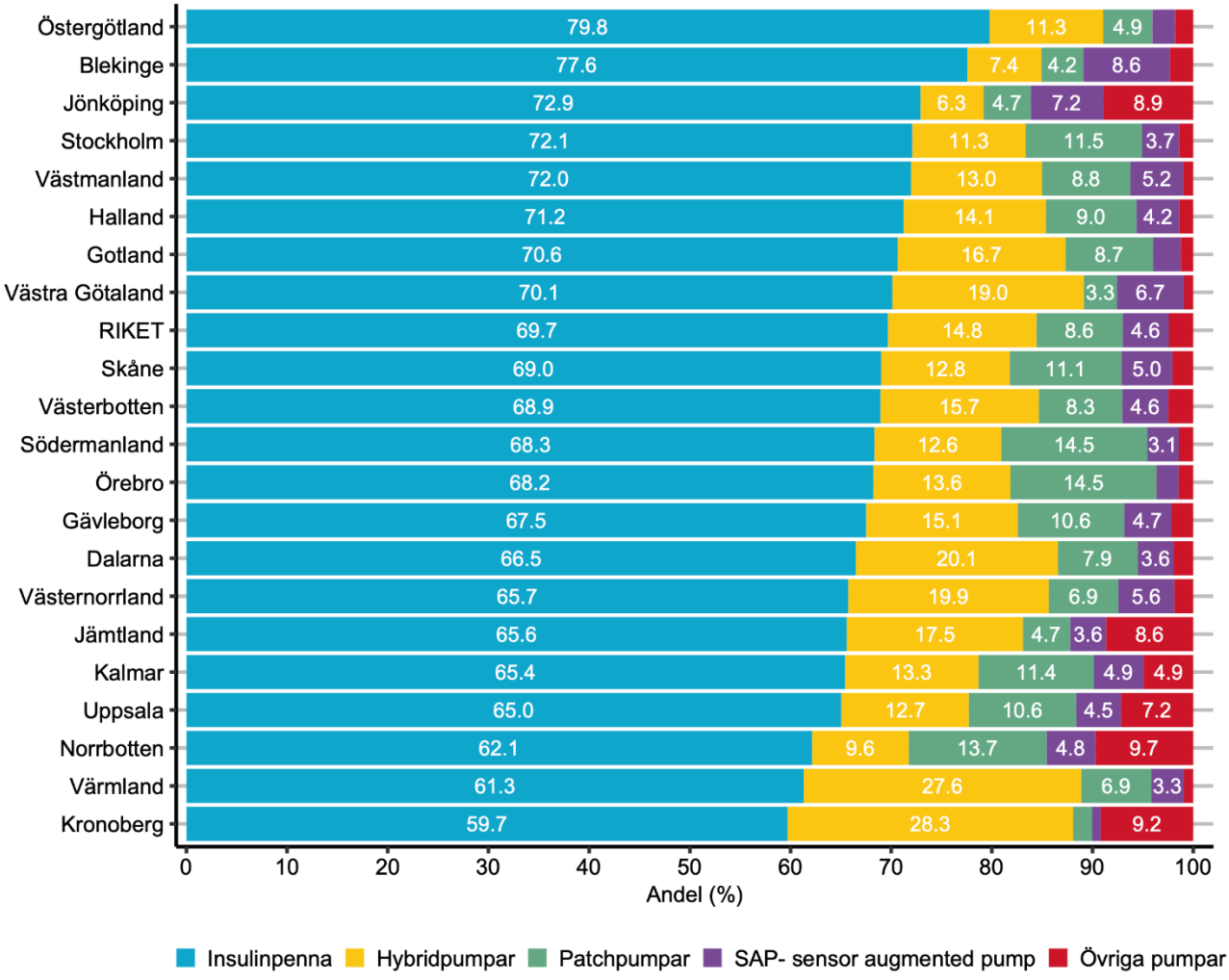
Patients not reaching desired clinical goals on optimal treatment with MDI and sensor are today considered for insulin pump therapy. Insulin pump therapy has the potential to optimise glycaemic control and for designated patients to reduce the daily treatment burden. Health care professionals carefully assess both risks and benefits of insulin pump therapy for the individual diabetes patient. The final decision to start with an insulin pump is made by the patient since insulin pump therapy is more challenging, with more technology for the patient to handle and more equipment to wear. Structured start and follow-up are initiated according to local routines.

Number of patients per year who undergo current treatment regimen

There has been a steady but not very steep increase in adult insulin pump users over the years, with 23% of adults with type 1 diabetes using insulin pump in 2018 to 30% in 2022. The proportion of pump users is higher in younger patients with 40% pump users among 18-40 years old, in both Sweden and in Region Västra Götaland, reflecting to some extent the high use of insulin pumps in

children with type 1 diabetes. Type 1 diabetes is a chronic disease, and many patients continue to be pump users into old age. In the upcoming Swedish National Diabetes Register annual report 2022 (NDR, 2023) the use of a hybrid closed loop insulin pump among adults with type 1 diabetes in Sweden varies from below 10% to over 30% in different regions (Figure 1).

Figure 1. The proportions of adults with type 1 diabetes using MDI with insulin, hybrid closed loop insulin pumps, patch insulin pumps (wireless), sensor augmented pumps (SAP) or other insulin pumps in Sweden (RIKET) and in the different regions of Sweden 2022 (NDR, 2023).



Blue = multiple daily injections with insulin, yellow = hybrid insulin pumps, green = patch pumps, purple = SAP, red = other pumps

Present recommendations from medical societies or health authorities

In the Swedish national guidelines on diabetes care (2018) from the National board of health and welfare, insulin pump therapy is recommended in patients with type 1 diabetes and recurrent events of hyper- and hypoglycaemia. Sensor augmented pumps (SAP) with or without predicted low glucose suspend (also known as predicted low glucose management) have been given a higher priority (priority 4) than insulin pump without sensor augmentation (priority 5) (Socialstyrelsen, 2018). The hybrid closed loop pump is a further development of the SAP and can both increase and stop insulin infusion in response to sensor glucose levels. In the next generation of automated insulin devices, the hybrid closed loop algorithms also have the possibility to administer automated correction bolus doses, in this report referred to as advanced hybrid closed loop (AHCL) system.

6. Health technology at issue: Advanced hybrid closed loop (AHCL) insulin pumps

The insulin pump technology has developed from devices with continuous subcutaneous insulin infusion to SAP with the ability to suspend insulin infusion and to communicate with a sensor, and further on to hybrid closed loop pumps. The first regulatory approval for hybrid closed loop insulin pumps, with automated administration of basal insulin came in 2018 in Europe (Garg et al., 2017, Garg and Shah, 2019) and were introduced in 2018 to patients with type 1 diabetes in Sweden. Patients using hybrid closed loop insulin pumps still need to administer insulin bolus doses before meals, by informing the system regarding the amount of carbohydrates they are planning to ingest.

Since the first hybrid closed loop insulin pump entered the market, several insulin pumps with automated basal insulin algorithms, either embedded in the pump or as a smartphone app, have been approved and are currently used globally as well as in Sweden. Some of the algorithms can also add automated correction bolus doses in between meals and are referred to as AHCL system (Collyns et al., 2021, de Portu et al., 2022, Leelarathna et al., 2021). This means that the algorithm by itself can correct a glucose level outside the target range without the involvement of the patient, thus relieving some of the extensive self-management burden from the patient. The algorithm can also help the patient achieve an optimal glucose control that can mitigate the risk of hypoglycaemia and hyperglycaemia. Based on previous extensive knowledge of the importance of glycaemic control in type 1 diabetes it is also reasonable to believe that the improved glycaemic control will lead to fewer long-term complications (DCCT, 1993, Nathan et al., 2005, Lind et al., 2014)

In 2023 two of these AHCL insulin administration systems are reimbursed in Region Västra Götaland, but this may change in the future since more systems are awaiting approval. Table 1 summarizes the differences in the functions of AHCL and Open loop/SAP systems.

Table 1. An overview of the difference between the systems in the intervention-group and the open-loop systems used as controls in comparison C2.

Function	**Advanced hybrid closed loop** Automatic basal insulin, automatic bolus corrections at high sensor glucose levels and manual meal boluses.	**Open loop/SAP** Pre-programmed basal insulin, manually increased or decreased basal insulin, no automatic bolus corrections, manual meal boluses. Sensor augmented pumps (SAP) may include low glucose suspend and predictive low glucose suspend function
Meal bolus	Manually	Manually
Reduce basal insulin	Automatic	Manually
Stop basal insulin	Automatic	Manually or Automatic (only SAP including predictive low glucose suspend and low glucose suspend)
Increase basal insulin	Automatic	Manually
Insulin correction bolus at high blood glucose levels	Automatic	Manually

7. Focused question

Does the use of advanced hybrid closed loop insulin pump system, compared with multiple daily injections with sensor based continuous glucose monitoring or a more traditional insulin pump (sensor augmented pump or separate pump and sensor), improve blood glucose control and quality of life and reduce the risk of diabetes complications in adults with type 1 diabetes, without compromising safety?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome	
P	Adults over 18 years of age with type 1 diabetes
I	Insulin delivery system with advanced hybrid closed loop (AHCL) defined as follows: -Automatically reduces, increases or stops basal insulin -Automatically provides insulin correction bolus at higher blood glucose -Patients still need to manually give meal boluses, Used for at least 2 weeks in daily life*, with 24 hours use Commercially available systems only, early do-it-yourself systems are excluded
C1	Manual insulin administration via multiple daily injections (MDI) combined with sensor based continuous glucose monitoring
C2	Insulin administration via insulin pump with integrated or separate sensor based continuous glucose monitoring with the following characteristics: -Cannot automatically increase or decrease basal insulin supply -Cannot automatically give insulin correction bolus at higher blood glucose - Patients still need to manually give meal boluses Pumps with the ability to automatically stop basal insulin at low glucose levels (predictive low glucose suspend) to avoid hypoglycaemia are included
O	*Critical for decision-making* Mortality Angiopathy: -Macroangiopathy (ischemic heart disease, stroke, claudication) -Microangiopathy (retinopathy, nephropathy, neuropathy) Emergency events: -Events of diabetic ketoacidosis -Events of severe hypoglycaemia HbA1c (an overall measure of glycaemic control) Health-related quality of life measured with validated instruments *Important for decision-making* Sensor related glucose control: -Time in range (TIR) -Time below range (TBR) (Hypoglycaemia) -Time above range (TAR) (Hyperglycaemia) - Glucose variability Patient reported outcomes with validated instruments, ex: - Sleep - Depression - Distress - Hypoglycaemia fear - Satisfaction Adverse events (ex. Insulin administration related complications)

*Time in range, time below range and time above range are clinically often observed over a period of 2 weeks

Definitions of outcomes

Angiopathy

Angiopathy includes macroangiopathy (ischemic heart disease, stroke, claudication) and microangiopathy (retinopathy, nephropathy, neuropathy).

Emergency events

Severe hypoglycaemia - defined as a hypoglycaemic event requiring assistance from another person- and ketoacidosis were regarded as emergency adverse events.

Glycated Haemoglobin (HbA1c)

According to the Swedish national guidelines on diabetes care from the National board of health and welfare (Socialstyrelsen, 2018), the target of optimal glycaemic control is <52 mmol/mol (corresponds to 6.9%-units)*. In the National Institute for Health and Care Excellence (NICE, 2015) in the United Kingdom (UK) the target level of HbA1c is 48 mmol/mol (6.5%-units) or lower, and the HbA1c should be measured every 3-6 months in adults with type 1 diabetes. The American Diabetes Association (2023) have a target level for HbA1c of <7%-units (53 mmol/mol) in type 1 diabetes and measure of HbA1c 1-2 times per year but more often when treatment is intensified to optimize control. Minimal important difference for HbA1c is considered to be a 0.5%-unit (5.5 mmol/mol) (Lenters-Westra et al., 2014). In some studies, HbA1c is expressed as mmol/mol, the unit we use in Sweden, and in other studies as %-units.

International federation of clinical chemistry: HbA1c 52 mmol/mol corresponds to 6.9% units in HbA1c National glycohemoglobin standardization program (%-units) (Socialstyrelsen, 2018). National glycohemoglobin standardization program = (0.09148 International federation of clinical chemistry) + 2.152 (National Glycohemoglobin Standardization Program, c2010).

Sensor related measurements

For this report sensor glucose is presented and levels are recalculated into the unit used in Sweden (mmol/L). However, the original units used by the authors are presented in Appendix (e.g. mg/dl). For conversion see Table 2.

TIR is defined as the percentage of time spent in a certain range of blood glucose concentration, usually 3.9-10.0 mmol/L, but may also be measured within a narrower range, e.g. 4.4–7.8 mmol/L or 3.9-8.0 mmol/L. TBR denotes the percentage of time spent below a certain range of blood glucose concentration, usually <3.9 mmol/L, but may also involve lower ranges/limits. Time above range (TAR) denotes the percentage of time spent above a certain range of blood glucose concentration, usually >10.0 mmol/L but may also be based on higher ranges/limits.

Table 2. Blood glucose levels in mmol/L and mg/dL from the included studies.

Glucose levels in mmol/L	Glucose levels in mg/dL
2.8	50
3.0	54
3.3	60
3.5	63
3.9	70
3.9-8.0	70-145
4.4–7.8	80-140
3.9-10.0	70-180
10.0	180
13.9	250
16.7	300

mmol/L: millimole per liter, mg/dL: milligram per deciliter.

There is an international consensus on target levels of sensor derived measures in clinical use. A guidance on targets for assessment of glycaemic control for adults with type 1 or type 2 diabetes came from the Advanced Technologies & Treatments for Diabetes (ATTD) Congress 2019 (Table 3). Each 5%-unit increase in time in range is considered to be associated with clinically significant benefits (Battelino et al., 2019).

Table 3. Guidance on targets for assessment of glycaemic control for adults with type 1 diabetes from the Advanced Technologies & Treatments for Diabetes (ATTD) Congress 2019 (Battelino et al., 2019)

Time in range		Time below range		Time above range	
Range	**Time per day**	**Lower limit of Range**	**Time per day**	**Upper limit of Range**	**Time per day**
3.9–10.0 mmol/L	>70%	<3.9 mmol/L	<4%	>10.0 mmol/L	<25%

mmol/L: millimole per liter.

The coefficient of variation of glucose variability is defined as SD of blood glucose divided by mean glucose and is expressed as a percentage in the majority of the included studies, higher values denoting a higher variability in the blood glucose level. The International consensus target level of glucose variability (% coefficient of variation) is less or equal to 36% (Battelino et al., 2019).

Health related quality of life and patient satisfaction measurements

Table 4. The span and polarity of the different scales

Outcome	Scale/Score	Explanation
The Diabetes Quality of Life questionnaire	0-100	Five domains: treatment satisfaction, treatment impact, social worry, diabetes worry, general well-being. The answers are ranged on a 5-point likert scale from very satisfied (1) to very dissatisfied (5). Each domain has a separate score that can be summarized in a total score, the total of the items of each scale being divided by the number of rated items. A higher total score means better quality of life. (Choudhary et al., 2022, DCCT Research Group, 1988, Jacobson et al., 1994)
Center for Epidemiological Studies Depression Scale- Revised (CESD-R)	0-60	A survey consisting of 20 items. Higher scores indicate more depressive symptoms (Bisio et al., 2021)
Diabetes Distress Survey (DDS)	1-6	A questionnaire with 28 items for adults. There are seven subscales. Higher scores indicate more distress (Kudva et al., 2021)
Diabetes treatment satisfaction questionnaire (DTSQ) ● Status ● Change	Total 0-36 ● 0-36 ● -18 to 18	Higher scores are positive (Boscari et al., 2022, Wheeler et al., 2022)
Hypoglycaemia Fear Survey (HFS-II) ● Behaviour subscale ● Worry subscale	Total 0–132 ● 0–60 ● 0–72	23 items for adults Higher total score indicates greater fear. Higher behaviour scores indicate greater tendency to avoid hypoglycaemia. Higher worry scores indicate more worry (Kudva et al., 2021, Lam et al., 2017)
INSPIRE	0-100	A questionnaire that measures a user's experience with automated insulin delivery technology. The adult questionnaire contains 22 items and are rated on a 0-4 scale which are calculated to obtain a 0-100 scale. Higher score is more positive (Kudva et al., 2021)
Pittsburgh Sleep Quality Index (PSQI)	0-21	a questionnaire consisting of ten items which assess sleep, including quality, disturbance, and medication, over the last month. Lower scores indicate better sleep (Bisio et al., 2021, Boscari et al., 2022)
Visual Analogical Scales: -Satisfaction -Difficulty of use -Satisfaction to wear	0-10	Higher scores are more positive (Benhamou et al., 2019)

Adverse events
In this report we have included all adverse events reported in the studies, even those unlikely to be related to the study technology and type 1 diabetes.

8. Methods

Systematic literature search (Appendix 1)
During May 2022, with an update in December 2022, two authors (TS, IS) performed systematic searches in Medline, Embase, and the Cochrane Library. The websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Services and Folkehelseinstituttet were visited. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. All abstracts were screened using the Rayyan tool. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. At least two authors read these articles independently of one another and it was finally decided in consensus which articles should be included in the assessment.

Critical appraisal and certainty of evidence
Randomised controlled trials (RCTs) (no limitations regarding sample size), non-randomised studies (n>10 in each group), and case series above a defined sample size (n>100, only complications/adverse events) were eligible for inclusion. In Appendix 2 the characteristics of the included trials are presented, and in Appendix 3 the excluded trials and the reasons for exclusion are presented. A checklist for assessment of RCTs, modified from the Swedish Agency for Health Technology Assessment and Assessment of Social Services by Health Technology Assessment (HTA) centrum (Checklist, 2021), was used to critically appraise the included trials. A checklist for assessment of non-randomised studies, provided by Swedish Agency for Health Technology Assessment and Assessment of Social Services, was used to critically appraise the included non-randomised studies. In Appendix 4 all the results and the assessed quality of each article have been summarised per outcome. The certainty of evidence was defined according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system per outcome (Atkins et al., 2004; GRADE Working group).

In Summary-of-findings tables (pages 11-15), a summary result per outcome and the associated certainty of evidence are presented.

Data extraction and analysis
One author extracted the data and another author checked for accuracy. Data per outcome was pooled in meta-analysis if possible, using a random effects model in RevMan 5.4 and presented as forest plots. Point estimates are presented as mean difference (MD) with 95% confidence interval (CI). Continuous data originally presented as median and interquartile range was transformed, assuming normal distribution, into mean and standard deviation (SD). The RCTs used either a cross-over design in the statistical analysis or the more orthodox parallel design with a common timeline. These two types of designs were assessed as subgroups in the meta-analyses. Only cross-over studies using appropriate statistical methods to handle the repeated measurements within patients were included in the meta-analyses.

Exploratory subgroup analyses were performed on the high-risk population targeted in Anderson (2019a), regarding the outcomes TIR, TBR, and time above range (TAR).

Ongoing research

A search in Clinicaltrials.gov (01 Dec 2022) using the search terms *"artificial pancreas" OR "bionic pancreas" OR "automated pancreas" OR "closed loop" OR closedloop OR Medtronics OR MiniMed OR Omnipod OR Tandem OR Dana | diabetes OR diabetic OR DM1 OR "DM 1" | Adult, Older Adult* identified 671 trials. A search in WHO International Clinical Trials Registry Platform (01 Dec 2022) using the search terms *("artificial pancreas" OR "bionic pancreas" OR "automated pancreas" OR "closed loop" OR closedloop OR Medtronics OR MiniMed OR Omnipod OR Tandem OR Dana) AND (diabetes OR diabetic OR DM1 OR "DM 1")* identified 457 trials. In total 802 unique ongoing trials were identified.

Patient involvement

The relevance of the outcomes included in the PICO have been confirmed by a patient representative. The patient representative also read and commented on the Swedish summary.

9. Results

Search results and study selection (Appendix 1)

The literature search identified 2,745 records after removal of duplicates. After reading the abstracts 2,491 records were excluded. Another 97 articles were excluded by two authors after reading the articles in full text. The remaining 157 articles were sent to all participants of the project group, and 15 articles (ten RCTs and five non-randomised studies) were finally included in the assessment (Appendix 2).

No data were identified for the two outcomes mortality and angiopathy regarding either of the comparison groups

Comparison advanced hybrid closed loop versus multiple daily injections with insulin (C1)

Included studies

One RCT was included for this comparison (Choudhary et al., 2022, Appendix 2). This trial included 82 adults over 18 years of age with type 1 diabetes. More details are published in de Portu et al. (2022). The trial was conducted in France, Germany, and in the UK.

Population

All participants had an increased HbA1c at baseline, which increases the risk for diabetic complications. The AHCL group had an initial HbA1c of mean 74.9 (SD 10.64) mmol/mol (mean 9.00 %-units [SD 0.97]) and the multiple daily injection group had an initial HbA1c of mean 75.7 (SD 7.83) mmol/mol (mean 9.07 %-units [SD 0.72]) at baseline. HbA1c is described as either mmol/mol or %-units, where the target of optimal glycaemic control is <52 mmol/mol (corresponds to 6.9%-units).

Intervention

Trial participants were either randomised to receive treatment with AHCL (intervention) or MDI with insulin and intermittent scanning sensor glucose monitoring (isCGM) and the groups were followed for 6 months. The AHCL group used a MiniMed 670 (version 4.0, Medtronics) insulin pump with an AHCL algorithm. The multiple daily injection group instead injected themselves with subcutaneous insulin several times per day.

Directness, study limitation, and precision

Study limitations included: some possible selection bias, the trial being unblinded, unclear ITT analysis, patient reported outcomes being subjective, and a substantial involvement of the manufacturer. Medtronics funded the study but were also part of the design, collection of data, study conduct, and data analysis.

Regarding precision, there was only one study with relatively few participants, wide confidence intervals for the patient reported outcomes and a wide SD for other outcomes.

Results per outcome

Critical for decision making

Mortality: No data was identified

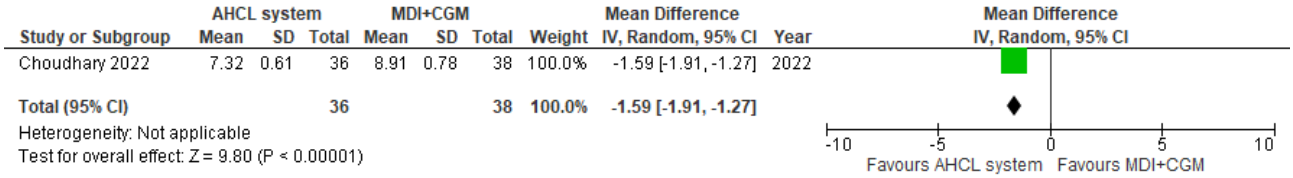
Angiopathy: No data was identified

Emergency events (Appendix 4.1)
Data was available for 75 of 82 participants. There were no cases of severe hypoglycaemia or ketoacidosis in either of the groups.

Conclusion: It is uncertain whether there is any difference in emergency events after 6 months, when comparing AHCL with MDI+sensor, in an adult population with type 1 diabetes and uncontrolled HbA1 (no GRADE assessment, due to lack of events).

HbA1c, mmol/mol or %-units (Appendix 4.2)
Data was available for 74 of 82 participants. In the AHCL group, the participants HbA1c decreased from mean 9.00 %-units (SD 0.97) (mean 74.9 mmol/mol) to mean 7.32 %-units (SD 0.61) (mean 57 mmol/mol) after 6 months. In the MDI+sensor group, HbA1c decreased from mean 9.07 %-units (SD 0.72) (mean 75.7 mmol/mol) at baseline to mean 8.91 %-units (SD 0.78) (mean 74 mmol/mol) after 6 months (Figure 2). The result showed a more pronounced decrease in HbA1c in the AHCL group expressed as change since baseline (Appendix 4.2).
(The target of optimal HbA1c is <52 mmol/mol (corresponds to 6.9%-units).

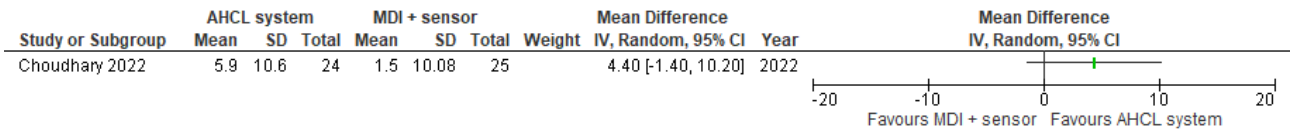
Figure 2. Outcome: HbA1c after 6 months, %-units



Conclusion: AHCL may result in a larger reduction in HbA1c after 6 months, when compared with MDI+sensor, in an adult population with type 1 diabetes and a substantially elevated baseline HbA1c (GRADE ⊕⊕◯◯).

Health-related quality of life measured with validated instruments (Appendix 4.3)
Data was available for 32-49 of 82 participants (depending on domain in the questionnaire). Changes in The Diabetes Quality of Life Questionnaire scores from baseline were only available for France and the UK. There was no statistically significant difference between the groups (Figure 3). Domain scores were also available for this questionnaire (Appendix 4.3).

Figure 3. Outcome: Change in Diabetes Quality of Life since baseline



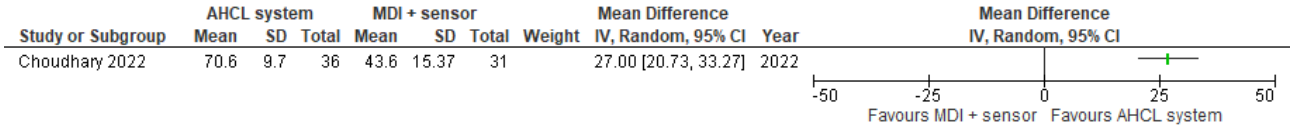
Conclusion: It is uncertain whether there is any difference in quality of life after 6 months, when comparing AHCL with MDI+sensor, in an adult population with type 1 diabetes and substantially elevated baseline HbA1c (GRADE ⊕◯◯◯).

Outcomes, important for decision-making

Time in range (TIR), %-unit (Appendix 4.4)

Data was available for 67 of 82 participants. Time in range 3.9-10.0 mmol/L was substantially higher in the AHCL group compared with the MDI group (Figure 4).

Figure 4. Outcome: Time in range, %-unit

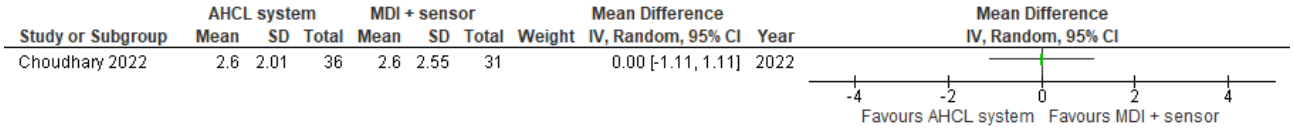


Conclusion: AHCL may lead to an increased time in range after 6 months, when compared with MDI+sensor, in an adult population with type 1 diabetes and substantially elevated baseline HbA1c (GRADE ⊕⊕◯◯).

Time below range (TBR) (Hypoglycaemia), %-units (Appendix 4.5)

Data was available for 67 of 82 participants. There was no significant difference between the AHCL group and the MDI group regarding time below 3.9 mmol/L (Figure 5). Neither was there any significant difference between groups regarding time below 3.0 mmol/L (Appendix 4.5).

Figure 5. Outcome: Time below 3.9 mmol/L, %-units

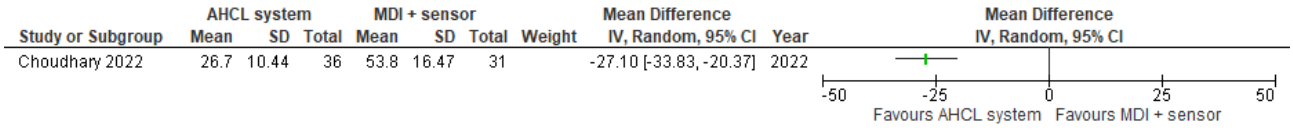


Conclusion: There may be little or no difference in time below range after 6 months, when comparing AHCL with MDI+sensor, in an adult population with type 1 diabetes and substantially elevated baseline HbA1c (GRADE ⊕⊕◯◯).

Time above range (TAR) (Hyperglycaemia), %-units (Appendix 4.6)

Data was available for 67 of 82 participants. Time above 10.0 mmol/L was substantially decreased in the AHCL group compared with the MDI group (Figure 6). Time above 13.9 mmol/L was also decreased in the AHCL group compared with the MDI group (Appendix 4.6).

Figure 6. Outcome: Time above 10.0 mmol/L, %-units

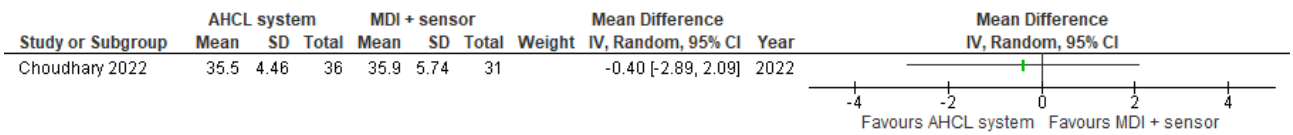


Conclusion: AHCL may lead to a decreased time above range after 6 months, when compared with MDI+sensor, in an adult population with type 1 diabetes and substantially elevated baseline HbA1c (GRADE ⊕⊕◯◯).

Glucose variability (Coefficient of variation of sensor glucose values), % (Appendix 4.7)

Data was available for 67 of 82 participants. There was no statistically significant difference in glucose variability/coefficient of variation between the AHCL group and the MDI group (Figure 7).

Figure 7. Outcome: Glucose variability % (Coefficient of variation of sensor glucose values)



Conclusion: There may be little or no difference in glucose variability after 6 months, when comparing AHCL with MDI+sensor, in an adult population with type 1 diabetes and substantially elevated baseline HbA1c (GRADE ⊕⊕◯◯).

Patient reported outcomes with validated instruments (Appendix 4.8)
Data was available for 73-74 (depending on instrument) of 82 participants. Patient-reported outcomes included change in Diabetes Treatment Satisfaction Questionnaire from baseline and change in Hypoglycaemia Fear Survey scores from baseline. There was a significantly greater treatment satisfaction and a greater decrease in fear of hypoglycaemia in the AHCL group (Figure 8-9, Appendix 4.8).

Figure 8. Outcome: Change in Diabetes Treatment Satisfaction Questionnaire scores since baseline

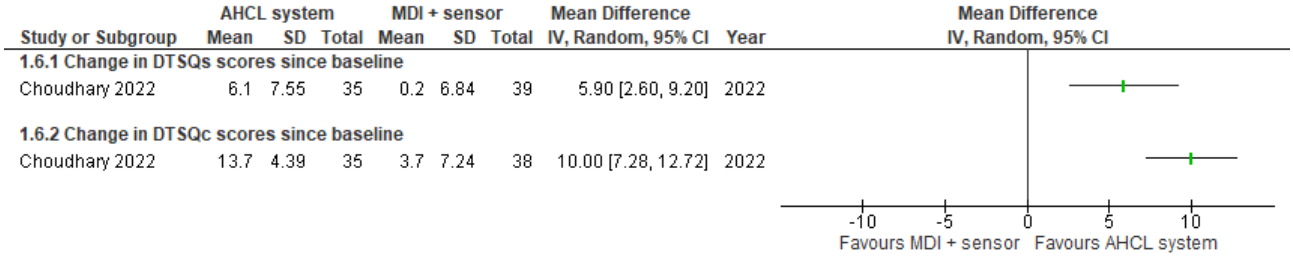
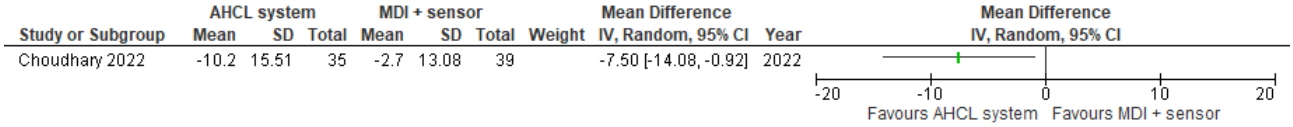


Figure 9. Outcome: Change in Hypoglycaemia Fear Survey scores since baseline



Conclusion: AHCL may lead to an increased diabetes treatment satisfaction and a small decrease in fear of hypoglycaemia after 6 months, when compared with MDI+sensor, in an adult population with type 1 diabetes and substantially elevated baseline HbA1c (GRADE ⊕⊕◯◯).

Adverse events (Appendix 4.9)
Data was available for 75 of 82 participants. In the AHCL group there were no events of diabetes-related hospitalizations or emergency room admissions, one serious adverse event unlikely to be related to the device (breast cancer), 66 non-serious adverse events where 15 were considered by the authors of being causally related to study device, and 56 device deficiencies (such as cannula site failure or a failure in communication between the insulin pump and the transmitter). In total 123 adverse events occurred during the 6-month follow-up. In the MDI%-units group there was one diabetes-related hospitalization and one emergency room admission, one serious adverse event (intra-vitreous haemorrhage), 39 non-serious adverse events where three were considered by the authors as being causally related to study device, and eight device deficiencies. In total 50 adverse events during the 6-month follow-up.

Conclusion: AHCL may lead to more non-serious adverse events after six months, when compared with MDI+sensor, in an adult population with type 1 diabetes and substantially elevated baseline HbA1c (GRADE ⊕⊕◯◯).

Comparison advanced hybrid closed loop versus insulin pump with integrated or separate sensor based continuous glucose monitoring (C2)

Included studies
For this comparison, nine RCTs (five with parallel design and four with cross-over design) (n=585 adults with type 1 diabetes) and five non-randomised studies (n=141 adults with type 1 diabetes) were included (Appendix 2). The included studies were conducted in several different countries, including UK, Germany, France, Italy, the US, and New Zealand.

Population
The population consisted of adults over 18 years of age with the diagnosis type 1 diabetes. Some studies only included the younger or older spectrum within this group. Most subjects were mixed-risk (varying levels of HbA1c), with one exception: the participants in Anderson et al. (2019a) were described as a high-risk population regarding risk of hypoglycaemia, due to the presence of hypoglycaemia unawareness.

Intervention
Participants in the intervention group used an AHCL system (different fabricants) and participants in the control group used an SAP system (open loop) with or without predicted low glucose suspend function (different fabricants). The time window (study period) varied from 2 weeks up to 6.5 months.

Directness, study limitations, and precision
Several of the included RCTs had some problems with directness. The RCTs with mixed age groups but with separate results for adults lacked some baseline information regarding the adult group. One RCT had a high-risk population regarding hypoglycaemia (Andersson et al., 2019a), another had a selected patient group with young adults only (Isganaitis et al., 2021). In one RCT, presented in several studies (Kudva et al., 2021, O`Malley et al., 2021), adults were part of both the adolescent and the adult group. Regarding study limitations, all RCTs lacked blinding of participants and staff and industry-involvement of authors was common. Three RCTs had unclear randomisation procedures (Andersson et al., 2019a, Collyns et al., 2021, Wheeler et al., 2022), and one RCT had insufficient info and statistical calculations for outcomes in the adult subgroup (Isganaitis et al., 2021). Two RCTs included patient reported outcomes with subjective components which is problematic in an open study (Kudva et al., 2021, Wheeler et al., 2022). Regarding precision, power was not separately calculated for the adult group in the mixed age studies (Collyns et al., 2021, Isganaitis et al., 2021, Kovatchev et al., 2020a, Kudva et al., 2021, O`Malley et al., 2021, Wheeler et al., 2022). There was also a limitation in the statistical analysis of differences for outcomes in the adult group in two RCTs (Isganaitis et al., 2021, Kovatchev et al., 2020a). Several RCTs did not report CIs, and some had notably wide SDs.

The non-randomised studies had in general no problems with directness except for occasionally scarce baseline information. Regarding study limitations the studies were potentially limited by lack of blinding, by the industry-involvement of the authors, and by the lack of time controls. There were unclarities regarding statistical handling of uncertainties in some studies (Andersson et al., 2016, Bisio et al., 2021). In one study (Bisio et al., 2021) there was uncertainty about the measurement of side effects, and a moderately high dropout rate. Regarding precision, the population sizes were quite small. One study (Boscari et al., 2022) had a very heterogeneous population which made the presented negative data difficult to interpret.

Results per outcome

Outcomes, critical for decision-making

Mortality: No data was identified

Angiopathy: No data was identified

Emergency events (Appendix 4.1)
Data was available for 536 of 563 participants. Five RCTs (Andersson et al., 2019a, Benhamou et al., 2019, Collyns et al., 2021, Isganaitis et al., 2021, Kovatchev et al., 2020b) (n=226), four non-randomised studies (Andersson et al., 2016, Bisio et al., 2021, Boscari et al., 2022, Kovatchev et al., 2017) (n=89), and two case series (Beck et al., 2022, Kruger et al., 2022) (n=221), reported this outcome.

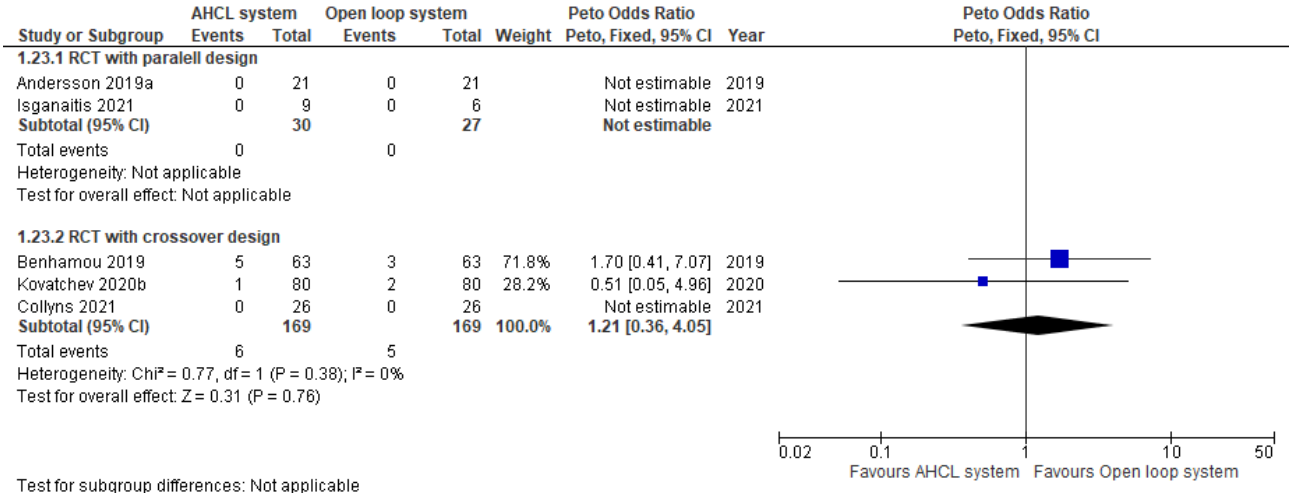
Events of diabetic ketoacidosis

No events of diabetic ketoacidosis were reported.

Events of severe hypoglycaemia

A meta-analysis of five RCTs, including 199 adult participants, showed no difference in the rate of severe hypoglycaemia, 6/199 vs 5/196. Peto Odds Ratio 1.21 % (95% CI 0.36 to 4.05) (Figure 10). The non-randomised studies reported no events of severe hypoglycaemia.

Figure 10. Outcome: severe hypoglycaemia



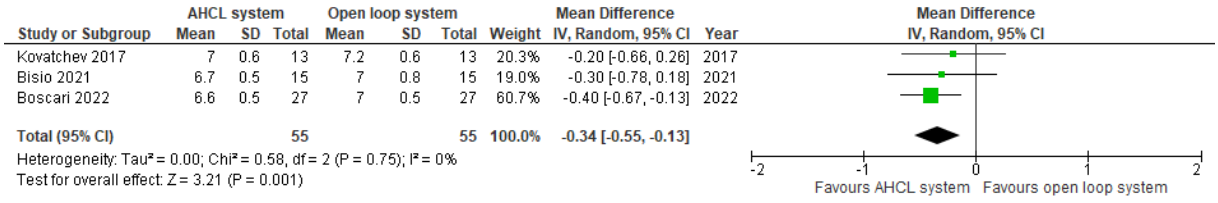
Conclusion: It is uncertain whether there is any difference in emergency events, when comparing AHCL with an open loop system, in a mixed risk adult population with type 1 diabetes (GRADE ⊕◯◯◯).

HbA1c, %-units (Appendix 4.2)

Data was available for 133 of 146 participants. Two RCTs (Benhamou et al., 2019, Isganaitis et al., 2021) (n=78) and three non-randomised studies (Bisio et al., 2021, Boscari et al., 2022, Kovatchev et al., 2017) (n=55), reported this outcome. Patients in the RCTs were followed for 3-6.5 months, while the participants in the non-randomised studies were followed for 1-5 months.

The two RCTs showed no statistically significant difference in the change in HbA1c between AHCL versus SAP. (Benhamou et al., 2019: mean difference: -0.15 [-0.33 to 0.03] %; Isganaitis et al., 2021: 0.14 [95% CI -0.96 to 1.24] %).

The three non-randomised (before/after) studies in contrast showed a small but statistically significantly larger decrease in HbA1c in the AHCL group (-0.34 [-0.55 to -0.13] %, p=0.001) (Appendix 5).



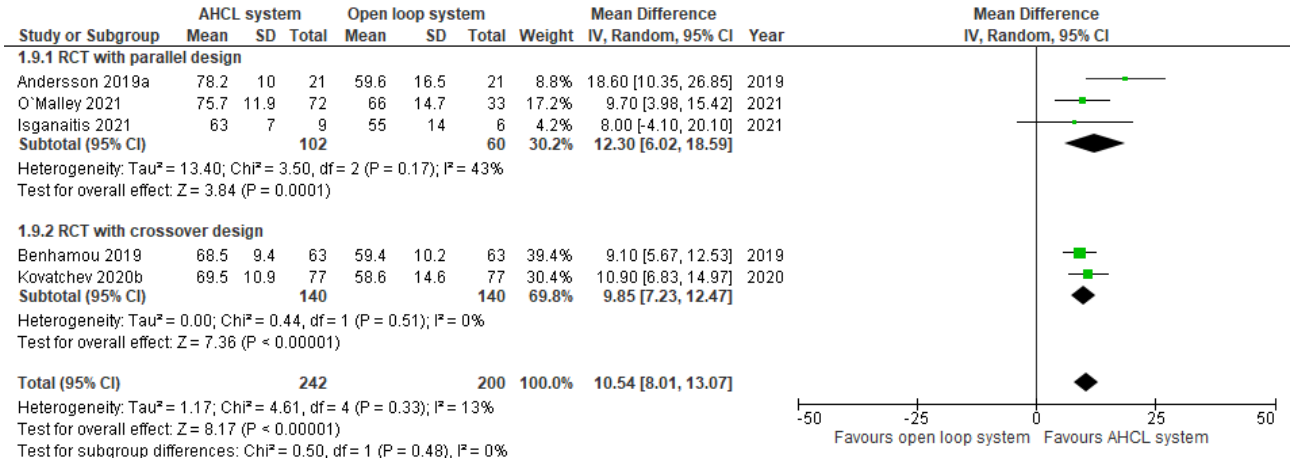
Conclusion: It is uncertain whether there is any difference in HbA1c, when comparing AHCL with open loop system, in a mixed risk adult population with type 1 diabetes (GRADE ⊕◯◯◯).

Health related quality of life measured with validated instruments (Appendix 4.3)
No data found.

Outcomes, important for decision-making

Time in range (TIR), %-units (Appendix 4.4)
Data was available for 453 of 495 participants. Six RCTs (Andersson et al., 2019a, Benhamou et al., 2019, Collyns et al., 2021, Isganaitis et al., 2021, Kovatchev et al., 2020b, O`Malley et al., 2021) (n=328) and five non-randomised studies (Andersson et al., 2016, Bisio et al., 2021, Boscari et al., 2022, Kovatchev et al., 2017, Toschi et al., 2022) (n=125) reported on sensor-based % time in range 3.9-10.0 mmol/l. The RCTs showed a significantly increased time in range 3.9-10.0 mmol/L in the AHCL group (+10.5 [95% CI 8.0 to 13.1] %, p<0.0001) (Figure 11). An exploratory subgroup analysis was performed on the high-risk population in Anderson (2019a), but exclusion of this population did not alter the result.

Figure 11. Outcome: Time in range 3.9–10.0 mmol/L, %-units



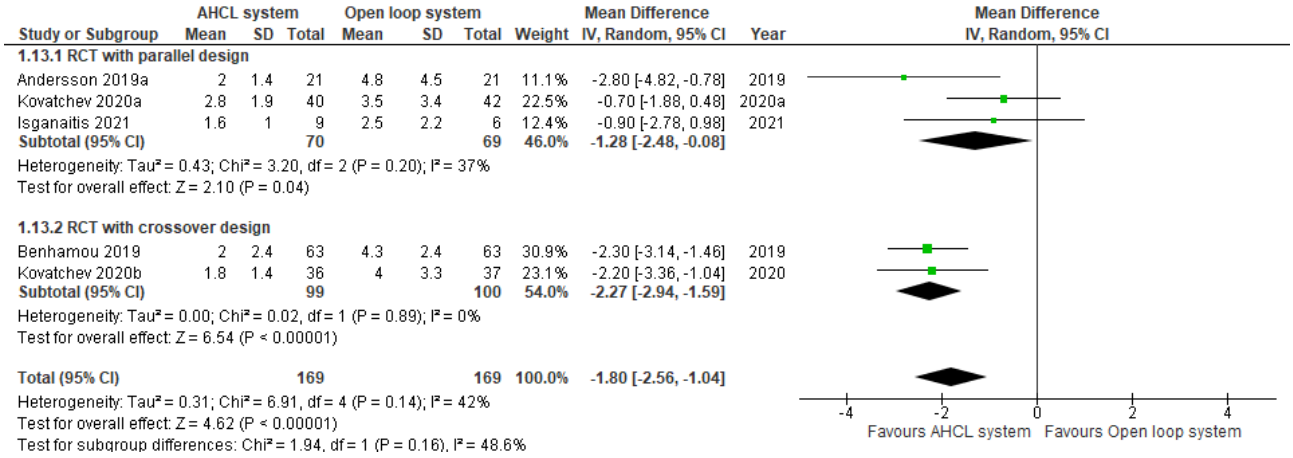
One RCT (Benhamou et al., 2019), with a total of 63 participants, also reported an increased time in the narrower range 4.4–7.8 mmol/L in the AHCL group (Appendix 4.4).

The non-randomised studies also showed increased time in range 3.9-10.0 mmol/L in the AHCL group. Boscari et al. (2022) also reported an increased time in the narrower range 3.9-7.8 mmol/L for the AHCL group (Appendix 4.4).

Conclusion: AHCL probably results in an increased TIR, when compared with the open loop system, in a mixed risk adult population with type 1 diabetes (GRADE ⊕⊕⊕◯).

Time below range (TBR) (Hypoglycaemia), %-units (Appendix 4.5)
Data was available for 430 of 472 participants. Six RCTs (Andersson et al., 2019a, Benhamou et al., 2019, Collyns et al., 2021, Isganaitis et al., 2021, Kovatchev et al., 2020a, Kovatchev et al., 2020b) (n=305) and five non-randomised studies (Andersson et al., 2016, Bisio et al., 2021, Boscari et al., 2022, Kovatchev et al., 2017, Toschi et al., 2022) (n=125) reported on sensor-based time below range. The RCTs showed a significantly decreased time <3.9 mmol/L in the AHCL group (-1.80 [95% CI -2.56 to -1.04] %, p<0.0001) (Figure 12). An exploratory subgroup analysis was performed on the high-risk population in Anderson (2019a) but did not alter the result.

Figure 12. Outcome: Time below range <3.9 mmol/L, %-units



A meta-analysis of two RCTs (n=105) showed decreased time < 3.5 or <3.3 mmol/L in the AHCL group (Appendix 5).

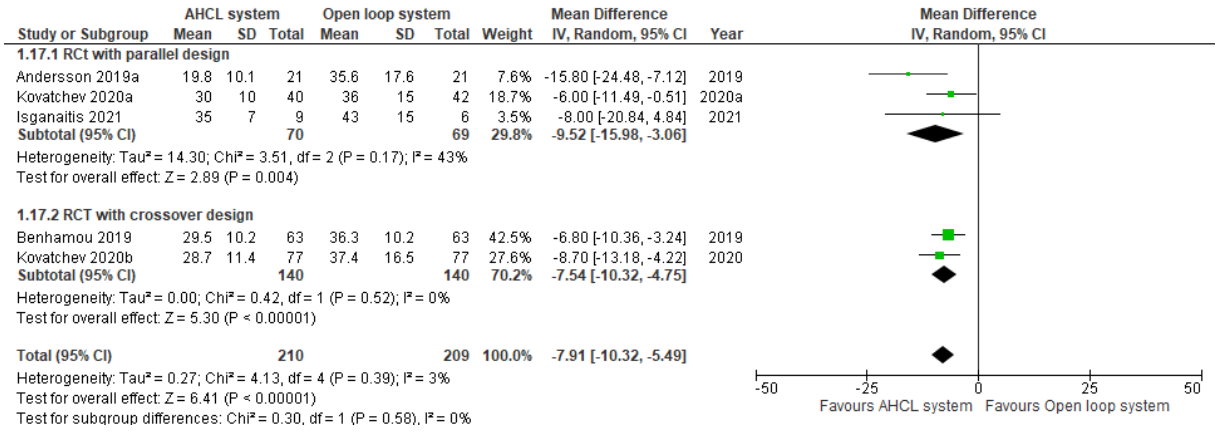
A meta-analysis of four RCTs (n=197) showed decreased time < 3.0 and <2.8 mmol/L in the AHCL group (Appendix 5).

Meta-analyses of two non-randomised studies (n=46) showed no group-difference in time <3.9 mmol/L or time <3.0 mmol/L (Appendix 5). The remaining three studies showed a decreased time <3.9 mmol/L in the AHCL group compared with the SAP group (Appendix 4.5)

Conclusion: AHCL probably results in a reduced amount of TBR, when compared with open loop system, in a mixed risk adult population with type 1 diabetes (GRADE ⊕⊕⊕◯).

Time above range (TAR) (Hyperglycaemia), %-units (Appendix 4.6)
Data was available for 430 of 472 participants. Six RCTs (Andersson et al., 2019a, Benhamou et al., 2019, Collyns et al., 2021, Isganaitis et al., 2021, Kovatchev et al., 2020a, Kovatchev et al., 2020b) (n=305) and five non-randomised studies (Andersson et al., 2016, Bisio et al., 2021, Boscari et al., 2022, Kovatchev et al., 2017, Toschi et al., 2022) (n=125) reported on sensor-based time above range. The RCTs showed decreased time >10.0 mmol/L in the AHCL group (Figure 13). An exploratory subgroup analysis was performed on the high-risk population in Anderson (2019a) but did not alter the result.

Figure 13. Outcome: Time above range >10.0 mmol/L, %-units



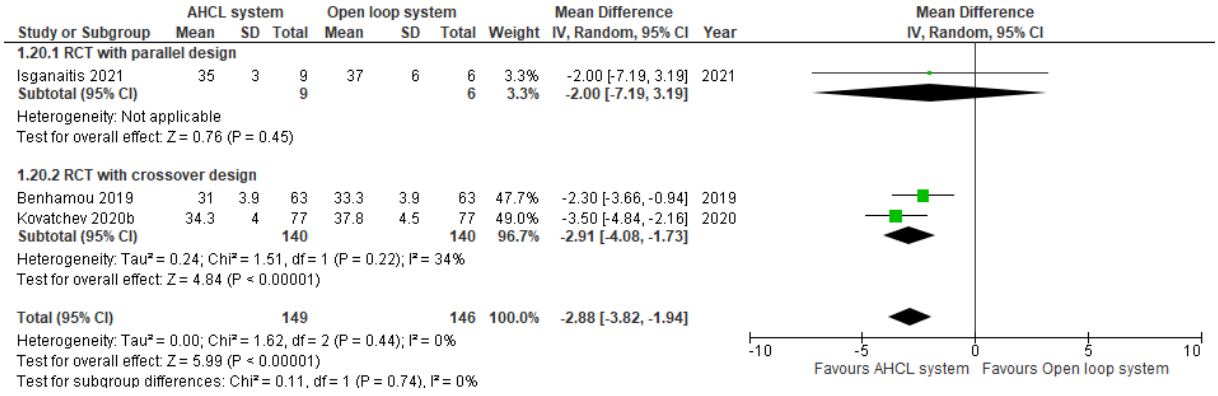
Meta-analyses of RCTs for time above range >13.3 or >13.9 mmol/L (n=197) and for time above >16.7 mmol/L (n=120) showed a decreased time above these ranges in the AHCL group (Appendix 5).

Meta-analyses of three non-randomised studies (n=83) showed decreased time >10 mmol/L and >13.9 mmol/L in the AHCL group (Appendix 5). The remaining two non-randomised studies showed a decreased time >10.0 mmol/L in the AHCL group (Appendix 4.6).

Conclusion: AHCL probably results in a reduced amount of TAR, when compared with open loop system, in a mixed risk adult population with type 1 diabetes (GRADE ⊕⊕⊕◯).

Glucose variability (Coefficient of variation of sensor glucose values), % (Appendix 4.7)
Data was available for 309 of 350 participants. Four RCTs (Andersson et al., 2019a, Benhamou et al., 2019, Isganaitis et al., 2021, Kovatchev et al., 2020b) (n=197) and four non-randomised studies (Andersson et al., 2016, Bisio et al., 2021, Boscari et al., 2022, Toschi et al., 2022) (n=112) reported on this outcome. The RCTs showed a statistically significantly decreased glucose variability in the AHCL group (Figure 14).

Figure 14. Outcome: Glucose variability (Coefficient of variation of sensor glucose values), %



A meta-analysis of the non-randomised studies also showed a decreased glucose variability in the AHCL group (Appendix 5).

Conclusion: AHCL may result in a reduced glucose variability, when compared with an open loop system, in a mixed risk adult population with type 1 diabetes (GRADE ⊕⊕◯◯).

Patient reported outcomes with validated instruments (Appendix 4.8)
Data was available for 256 of 266 participants. Three RCTs (Benhamou et al., 2019, Kudva et al., 2021, Wheeler et al., 2022) (n=210) and two non-randomised studies (Bisio et al., 2021, Boscari et al., 2022) (n=46) reported on these outcomes.

Pittsburgh Sleep Quality Index (PSQI)

A meta-analysis of two non-randomised studies (n=46) revealed no statistically significant difference between the groups: mean difference -0.28 (95% CI -1.40 to 0.83) (Appendix 5).

Center for Epidemiological Studies Depression Scale (CESD-R)

One non-randomised study (n=15) showed no statistically significant difference between the groups (Appendix 4.8).

Diabetes Distress Survey (DDS)
One RCT (n=119) reported no statistically significant difference between the groups (Appendix 4.8). One non-randomised study (n=15) reported a statistically significant lower distress (total score) in the AHCL group (Appendix 4.8).

Hypoglycaemia fear (HFS-II)
Two RCTs (n=147) reported no difference in hypoglycaemia fear between the groups (Appendix 4.8).

A meta-analysis of two non-randomised studies (n=46) showed no significant difference between the groups (Appendix 5).

Technology satisfaction
Two RCTs (n=92) and one non-randomised study (n=31) reported on Diabetes Treatment Satisfaction Questionnaire, consisting of status and change. The RCT Benhamou et al. (2019) showed no difference between the groups, while the RCT Wheeler et al. (2022) and the non-randomised study Boscari et al. (2022) showed a greater technology satisfaction in the AHCL group (Appendix 4.8).

One RCT (n=63) reported three Visual Analogical Scales: satisfaction, difficulty of use, satisfaction to wear. There was no statistically significant difference between the groups regarding satisfaction and satisfaction to wear, but AHCL was reported as more difficult to use (Appendix 4.8).

One RCT (n=119) reported no difference in user experience (INSPIRE) between the groups (Appendix 4.8).

Conclusion: It is uncertain whether there is any difference in patient reported outcomes, when comparing AHCL with open loop system, in a mixed risk adult population with type 1 diabetes (GRADE ⊕◯◯◯).

Adverse events (Appendix 4.9)
Data was available for 243 of 270 participants. Three RCTs (Andersson et al., 2019, Benhamou et al., 2019, Kovatchev et al., 2020b) (n=185) and three non-randomised studies (Andersson et al., 2016, Bisio et al., 2021, Kovatchev et al., 2017) (n=58) reported on adverse events other than severe hypoglycaemia or diabetic ketoacidosis (Table 5). Adverse events included infusion site reaction, hyperglycaemia, mild to moderate ketonemia and various types of device deficiencies.

Table 5. Adverse events (including device issues but excluding the emergency adverse events ketoacidosis and serious hypoglycemia, see above under separate headings)

Study	Study design	Number of participants	AHCL	SAP/open loop
Anderson et al., 2019a	RCT	42	14	10
Benhamou et al., 2019	RCT with cross-over design	63	9	0
Kovatchev et al., 2020b	RCT with cross-over design	80	20	0
Total		**185**	**43**	**10**
Anderson et al., 2016	Non-randomised study	30	0	0
Bisio et al., 2021	Non-randomised study	15	0	0
Kovatchev et al., 2017	Non-randomised study	13	2	0
Total		**58**	**2**	**0**

Conclusion: It is uncertain whether there is any difference in adverse events, when comparing AHCL with open loop system, in a mixed risk adult population with type 1 diabetes (GRADE ⊕◯◯◯).

10. Organisational aspects

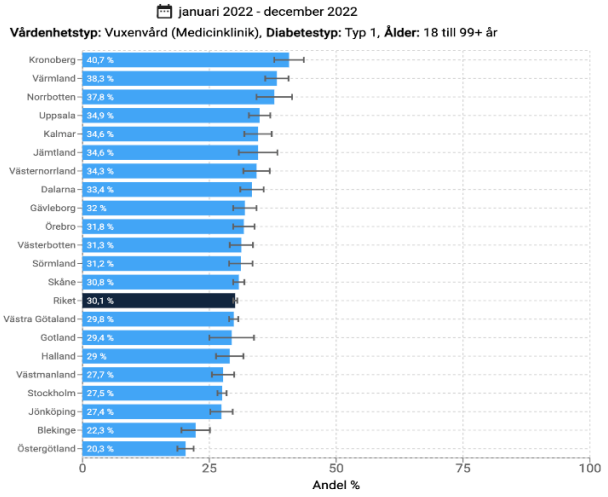
Time frame for the putative introduction of the new health technology

The health technology hybrid closed loop insulin pump (including both hybrid closed loop and AHCL), is already introduced and in 2022 and is used by approximately 1700 adult individuals with type 1 diabetes in the Region Västra Götaland.

Present use of the technology in other hospitals in Region Västra Götaland

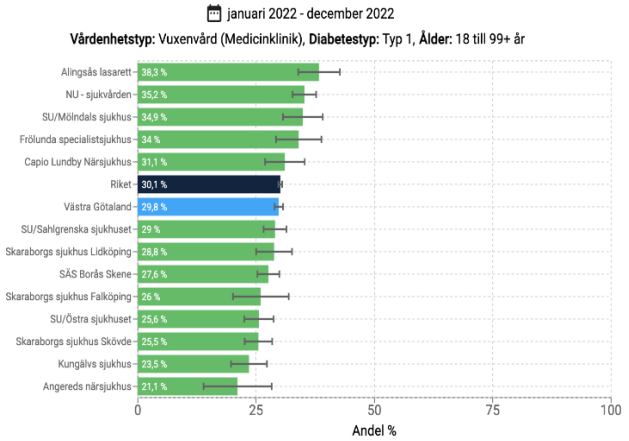
In Region Västra Götaland 63 percent of the pump users have a hybrid closed loop or AHCL insulin pump in 2022. According to the Swedish National Diabetes Register (2022) in Sweden as well as in Region Västra Götaland about 30 percent of adult patients with type 1 diabetes are insulin pump users (Figure 15, 16).

Figure 15. The proportion of adults with type 1 diabetes with insulin pump per region in Sweden 2022 (Knappen, [n.d.])



Namn	Antal patienter	Rapporterat indikator	Antal uppfyllda	Resultat (Andel %)	Konfidens-intervall (95%)	Medelålder
Kronoberg	1240	1074	437	40,7	37,8 - 43,6	49,1
Värmland	1809	1776	681	38,3	36 - 40,6	49,6
Norrbotten	742	730	276	37,8	34,3 - 41,3	47
Uppsala	2088	2046	714	34,9	32,8 - 37	48,3
Kalmar	1370	1227	424	34,6	31,9 - 37,3	48,4
Jämtland	607	596	206	34,6	30,8 - 38,4	48,1
Västernorrland	1310	1309	449	34,3	31,7 - 36,9	49,4
Dalarna	1592	1550	517	33,4	31,1 - 35,7	50,9
Gävleborg	1622	1600	512	32	29,7 - 34,3	49
Örebro	1842	1832	583	31,8	29,7 - 33,9	49,1
Västerbotten	1516	1504	470	31,3	29 - 33,6	45,3
Sörmland	1510	1501	468	31,2	28,9 - 33,5	49,6
Skåne	6346	6250	1925	30,8	29,7 - 31,9	48,4
Riket	50624	49856	15018	30,1	29,7 - 30,5	48,4
Västra Götaland	9039	8980	2676	29,8	28,9 - 30,7	48
Gotland	407	405	119	29,4	25 - 33,8	50,3
Halland	1054	1047	304	29	26,3 - 31,7	49,8
Västmanland	1524	1520	421	27,7	25,5 - 29,9	49,6
Stockholm	10351	10258	2824	27,5	26,6 - 28,4	47,4
Jönköping	1525	1517	416	27,4	25,2 - 29,6	49
Blekinge	826	820	183	22,3	19,5 - 25,1	51
Östergötland	2570	2558	518	20,3	18,7 - 21,9	47,2

Figure 16. The proportion of adults with type 1 diabetes with insulin pump in Region Västra Götaland, Sweden 2022 (Knappen, [n.d.])



Namn	Antal patienter	Rapporterat indikator	Antal uppfyllda	Resultat (Andel %)	Konfidens-intervall (95%)	Medelålder
Alingsås lasarett	478	475	182	38,3	33,9 - 42,7	48,4
NU - sjukvården	1447	1439	507	35,2	32,7 - 37,7	49,7
SU/Mölndals sjukhus	493	490	171	34,9	30,7 - 39,1	46,5
Frölunda specialistsjukhus	382	376	128	34	29,2 - 38,8	45,8
Capio Lundby Närsjukhus	463	460	143	31,1	26,9 - 35,3	45,2
Riket	50624	49856	15018	30,1	29,7 - 30,5	48,4
Västra Götaland	9039	8980	2676	29,8	28,9 - 30,7	48
SU/Sahlgrenska sjukhuset	1412	1398	406	29	26,6 - 31,4	48,6
Skaraborgs sjukhus Lidköping	551	548	158	28,8	25 - 32,6	49,6
SÄS Borås Skene	1403	1399	386	27,6	25,3 - 29,9	48,5
Skaraborgs sjukhus Falköping	215	215	56	26	20,1 - 31,9	50
SU/Östra sjukhuset	760	741	190	25,6	22,5 - 28,7	44,3
Skaraborgs sjukhus Skövde	876	874	223	25,5	22,6 - 28,4	47,9
Kungälvs sjukhus	487	486	114	23,5	19,7 - 27,3	49,4
Angereds närsjukhus	125	123	26	21,1	13,9 - 28,3	43,4

Consequences of the new health technology for personnel

In diabetes care there is and has always been a steady health technology development but during the last decade the progress has become more rapid. Therefore, the personnel working with diabetes technology needs continuous education and designated time to learn how to utilize the new systems for the greatest possible patient benefit and to share this knowledge with the patient. Since digital

care - including remote patient monitoring and video calls with patients - is becoming increasingly common in the evaluation of diabetes treatment, there is also a need for technical support to make digital care as smooth, effective, and safe as possible for both the patients and the staff.
To reach the full potential of the technical devices, new users of hybrid closed loop and AHCL insulin pumps need more time with the diabetes team during the first year, but in this process, they are also gaining new knowledge and insights which will likely pay off later in terms of reduced long-term complications.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

The differences in choices of treatment and medical support between out-patient clinics treating patients with type 1 diabetes in the Region Västra Götaland are small. Around-the-clock technical support of the insulin pumps is provided by the manufacturers and is included in the negotiated price.

11. Economic aspects

This health economic report consists of two parts. Firstly, a summary of cost-effectiveness studies conducted within the criteria of PICO and secondly, an estimation of costs of automatic insulin pumps for the patients of type 1 diabetes in Region Västra Götaland. This data of device and device maintenance have been retrieved from administrative databases of Region Västra Götaland in cooperation with clinicians actively working with insulin pump and relevant healthcare services, and it is presented here to illustrate the economic impact of a wider use of these techniques. The costs of health staff, namely doctors, nurses and dietitians were taken from the Kostnad per patient (KPP, Cost per patient) database with support from statisticians in the region.

Part 1: Summary of cost-effective analysis studies of automatic insulin pump

The PICO did not include health-economy outcomes, but three health economic studies found in the literature search were judged to be of relevance for predicting the economic consequences of a wider introduction. In two of the studies, a cost-effectiveness analysis was performed (Jendle et al., 2021, Lambadiari et al., 2022), while the third one was a systematic review of existing cost-effectiveness analyses carried out in high-income countries, like Sweden, but in both similar (United Kingdom) and different (The United States) health-care systems (Pease et al., 2020c).

To date we do not know the clinical consequences of a given reduction in the new surrogate variable TIR. The cost-effectiveness calculations referred here (Jendle et al., 2021 and Lambadiari et al., 2022) are based on assumed HbA1c-changes, found in observational studies (i.e. not RCTs) and a cross-over trial, all showing a benefit for the AHLC system. Extrapolation based on the known relationship between HbA1c and diabetic complications was then performed. In the present HTA analysis, when assessing only RCTs, a significant difference in HbA1c was only found in a high-risk diabetic population by the AHLC system and not in middle risk patients. Thus these calculation of QALY and ICER are less valid for our report but we still refer them in this report for completeness.

The study by Jendle et al. (2021) investigated the cost-effectiveness of the AHCL system MiniMed 780G (*intervention*) versus MDI with intermittent scanning sensor or insulin pump therapy with continuous subcutaneous insulin infusion (*comparison*) in people with type 1 diabetes in Sweden. Using a societal perspective in the analysis, the incremental cost-effectiveness ratio of this analysis was with this mode of calculation estimated to 430,663 SEK per QALY, which would be cost-effective since it is below the Swedish cost-effectiveness threshold of 500,000 SEK per QALY. While considering the direct cost only, MiniMed 780G system still appeared to be cost-effective

with an incremental costs-effectiveness ratio of 373,700 SEK. In the sensitivity analysis where the researchers changed the HbA1c benefit, the intervention remained cost-effective.

A study conducted by Lambadiari and colleagues compared the AHCL system MiniMed 780G (*intervention*) versus SAP system with predicted low glucose suspend (*comparison 1*) or MDI plus intermittent scanning sensor (*comparison 2*) in people with type 1 diabetes in Greece (Lambadiari et al., 2022). The intervention thus resulted in cost-savings (Incremental costs-effectiveness ratio = -36,307 SEK), the interpretation was that the intervention is cost-effective.

When comparing the intervention with comparison 2, the intervention is still cost-effective since the willingness to pay per QALY in Greece was 34,000 euro, and the likelihood of being cost-effective was 84.2%. The sensitivity analyses showed that some changes in some parameter values, like time horizon, fear of hypoglycaemia utility, severe hypoglycaemic event rate, and HbA1c reduction led to "not cost-effective" outcome.

Pease and colleagues conducted a systematic review and narrative synthesis of Cost-effectiveness of health technologies in adults with type 1 diabetes (Pease et al., 2020c). This review included 35 studies in several high-income countries like the United Kingdom, the Netherlands, Sweden, the United States, Canada, Australia and summarized the effects of continuous subcutaneous insulin infusion with combination of self-monitoring of blood glucose. Insulin pumps or glucose sensors per se appeared cost-effective, particularly in populations with higher HbA1c levels and rates of hypoglycaemia. However, cost-effectiveness for combined insulin pumps and glucose sensors (i.e. our topic) was less clear.

These QALY-calculations do however suffer from some serious limitation: they are based mainly on observational data and on expected HbA1c-reductions only, not on key clinical outcomes like mortality and various types of angiopathy.

The QALY calculations also include measurement of patient satisfaction. In the comparison multiple injections + sensor versus AHCL systems, we did observe an improvement of Patient satisfaction variables, but this was not consistently the case in the AHCL versus SAP comparison. The published QALY-calculations should therefore be interpreted with considerable caution.

For the present HTA report we therefore refrain from detailed QALY-calculations and just provide data regarding costs at varying degrees of hybrid system use in the current type 1 diabetes population, in VGR as well as nationally (Table 6).

Part 2: Costs of continuous insulin pump and daily insulin injection for patients with type I diabetes

Eight treatment options of supplying insulin to the patients have been identified by a group of experienced clinicians in Region Västra Götaland. While 6 of them (treatment options 1-6) used insulin pump, the other two (treatment options 7-8) use MDI with insulin and sensor. Costs of each intervention has been estimated by identifying the inputs and their magnitudes and then the monetary value can be calculated (Table 6). We have applied annuitization of capital items (for instance MiniMed 780G included Guardian link 4 with 4-year lifetime and 3% discounting rate) and used inflation-adjusted discounting rate to assess the costs at the price level of 2022. It should be noted that this calculation includes only the operational costs and was unable to consider the start-up or any sunk costs because of lack of data. Furthermore, the regional perspective, i.e., costs that have been borne only by Region Västra Götaland, have been considered.

Table 6. An example of estimated cost* per patient of continuous insulin pump and multiple daily insulin injections (Region Västra Götaland)

Intervention scenarios	(n= Estimated number of patients)	Costs per patient (SEK)*				
		Year 1	Year 2	Year 3	Year 4	Average cost per year
1) Patient with AHCL MiniMed 780G	1,708	88,619	71,594	62,864	52,086	68,791
2) Patient with AHCL Tandem t:slim X2 Control-IQ		98,547	76,029	70,143	64,072	77,198
3) Patient with SAP MiniMed 740G (previous 640G)	602	85,703	66,503	58,227	48,009	64,611
4) Patient with SAP Tandem t:slim X2 Basal- IQ		92,545	74,818	66,211	56,719	72,573
5) Patient with Omnipod DASH (patch pump) with Dexcom sensor**	297	90,171	71,815	61,399	48,761	68,037
6) Patient with Omnipod DASH (patch pump) with FreeStyle Libre 3 sensor**		66,538	48,206	41,214	32,581	47,135
7) Multiple daily insulin injections with Dexcom sensor	6,384	56,112	51,883	44,358	35,067	46,855
8) Multiple daily insulin injections with FreeStyle Libre 3 sensor		30,579	28,275	24,174	19,110	25,534

AHCL: Advanced hybrid closed loop, SAP: sensor augmented pump, SEK: Swedish krona
*At price level of 2022 and 3% discounting rate applied, **Not SAP or AHCL

A closer observation shows that one system, Sensors Dexcom G6 (change every 10 days), costs most (26,755 SEK). Tandem t:slim X2 Control-IQ which generates a capital input which costs annually 10,819 SEK. The costs of device incurred 14.0%, device and maintenance account for 66.0% of the total costs, while the staff costs account for 20.0% for this costliest treatment options. The staff costs which include the visits to doctor, nurse and dietitian have been estimated to 15,424 SEK each year over this 4-year period. This cost is higher (33,598 SEK) in the first year and reduced in the later years. Similar pattern of staff cost has been observed for other treatment options too, but more strongly for treatment options 1-6 since in the first year, more frequent nurse's visits are needed (5-8 visits across the treatment options).

On the contrary, the least costly intervention (treatment option8) MDI and sensor FreeStyle Libre 3 and total daily dose (TDD) insulin accounted annually for 10,638 SEK and 4,870 SEK respectively over a 4-year period. Device and maintenance costs 60.7% of the total costs, while the rest 39.3% covers the staff costs. It should be noted that the patients use the sensors FreeStyle Libre 3 in their own mobile phone.

In the cost calculation for all treatment options, we observed higher use of devices and maintenance in automated insulin pumps for treatment options 1-6 as well as higher use of staff for treatment options 1-2, which led to higher cost per patient. In appendix 6, detail of inputs and costs per patient of all treatment options are presented.

A total of 8,991 patients utilized any of the eight treatment options in 2022 in Region Västra Götaland. We have calculated the costs of the patient-cohort of year 2022 over four years by after merging the treatment options into four insulin providing treatment options (table 7). About 71% of the total patients utilized treatment options 7 and 8 together, while treatment options 1 and 2 were used together by 19% of the total patients. treatment options 3-4 (together) and 5-6 (together) were utilized by 6.7% and 3.3% of the total patients respectively. Considering the cost per patient for each of 8 treatment options and the distribution of the total patients across these treatment options, a total annual cost of approximately 414.1 million SEK has been estimated.

The largest annual total cost has been observed in patients with treat-ment options 7 and 8 (231.07 million SEK or 55.8% of annual total costs of the region) since it covers a high number of patients (6,384 or 71%) with a moderately relatively low cost per patient (Table 7).

Table 7. Estimated annual total costs* of all patients** for four main treatment options over four years and an estimated average cost per year (Region Västra Götaland)

Scenario	Insulin providing process (n=estimated number of patients)	Total costs in Million SEK for all patients per treatment option				
		Year 1	Year 2	Year 3	Year 4	Average cost per year
Treatment options 1 & 2	AHCL (n=1708)	159.8	126.1	113.6	99.2	124.7
Treatment options 3 & 4	SAP (n=602)	53.7	42.5	37.5	31.5	41.3
Treatment options 5 & 6	Omnipod DASH (patch pump) + sensor (n=297)	23.3	17.8	15.2	12.1	17.1
Treatment options 7 & 8	Multiple daily insulin injections + sensor (n=6384)	276.7	255.9	218.8	172.9	231.1
All scenarios	**8991**	**513.5**	**442.3**	**385.0**	**315.7**	**414.1**

AHCL: Advanced hybrid closed loop, SAP: sensor augmented pump, SEK: Swedish krona

*At price level of 2022 and 3% discounting rate applied, **Patient-cohort of 2022

The patients with treatment options 1 & 2 have the next larger costs of 124.7 million SEK (30.1%) of the total annual costs, followed by treatment options 3 & 4 with 41.3 million (10.0%) and treatment options 5 & 6 with 17.8 million SEK (4.1%). Either large number of patients or high cost per patient with these treatment options contribute high total costs.

It should be noted that some patients switched from one type of insulin pump to another during these four years, which could not be captured in the data. We, thus, had to take the assumption that the patients who started with a specific type of insulin pump continued with the same during entire period of analysis.

It is obvious that widespread implementation of automated insulin pump systems in treating type 1 diabetes patients will be a large cost for Region Västra Götaland. However, most T1D patients are already supplied with sensors and many patients have also become adapted to and are satisfied with autoinjections of insulin and hence are not motivated to switch to ADHL systems.

It seems likely that the use of AHCL systems will increase gradually, and this increased use will probably be accompanied by price reductions.

12. Ethical aspects

The ethical dilemma consists in weighing a likely but undocumented future reduction in diabetic complications against an immediate and very substantial displacement effect that will be generated by rapid transfer of a large number of patients from sensor-based penn injections to AHCL systems. According to the ethical Medical Need principle, priority should in this situation be given to patients not sufficiently well controlled by sensor + penn injection treatment.

13. Discussion

The aim of this HTA report was to compare advanced hybrid closed loop (AHCL) insulin pump systems with multiple daily injections with insulin in combination with sensor monitoring, or with open loop systems (SAP with or without predicted low glucose suspend) in adults with type 1 diabetes. The AHCL systems in this report was defined as a system with the possibility to administer autocorrection doses without patient interaction. There was only one trial comparing AHCL with multiple daily injections (MDI) with insulin and intermittent scanning sensor and 9 RCTs and 5 non-randomised studies comparing AHCL systems to open loop systems. Importantly, we did not find any studies reporting the key clinical outcomes mortality or micro- or macrovascular angiopathy.

Summary of main results

The main findings comparing AHCL with MDI+sensor with insulin in combination with continuous glucose monitoring in a high-risk population are:

- **It is uncertain** whether there is any difference in severe adverse events
- AHCL **may** result in a large reduction of HbA1c since baseline
- There **may** be little or no difference in quality of life
- AHCL **may** increase time in range
- AHCL **may** decrease time below range
- AHCL **may** decrease time above range
- There **may** be little or no difference in glucose variability
- AHCL **may** lead to increased treatment satisfaction and a greater decrease in fear of hypoglycaemia
- AHCL **may** lead to a greater number of non-severe adverse events

The main findings comparing AHCL with SAP with or without predicted low glucose suspend are:

- **It is unknown** if there is any effect on mortality or diabetic complications.
- **It is uncertain** whether there is any difference in severe adverse events or other adverse events. There were no events of severe diabetic ketoacidosis.
- **It is uncertain** whether there is any difference in HbA1c
- AHCL **probably** increases time in range
- AHCL **probably** decreases time below range
- AHCL **probably** decreases time above range
- AHCL **may** slightly reduce glucose variability
- **It is uncertain** whether there is any difference in patient reported outcomes

Effects of AHCL on HbA1c

In a glycaemic high-risk population, with mean baseline HbA1c of 75 mmol/mol, AHCL resulted in improved levels of HbA1c when compared with MDI and use of intermittent scanning sensor. In patients with both optimal and suboptimal baseline HbA1c, AHCL had uncertain effect on HbA1c when compared with SAP.

An observational study by Lind et al. showed that type 1 diabetes patients with HbA1c of 73-81mmol/mol had a four-fold increased risk of death from any cause and death from cardiovascular disease compared to matched controls. Noteworthy was that patients with HbA1c below 52 mmol/mmol still had a two-fold increased risk of mortality compared to the controls. (Lind et al., 2014)

Improvement of HbA1c is a cornerstone to prevent diabetes long-term complications and this has been well established in previous studies (DCCT, 1993, Nathan et al., 2005). To achieve an optimal

glycaemic control can be challenging for the patient. The insulin demand varies depending on the time of the day and days of the week and depends on factors such as stress, illness, physical activity and food intake.
To reach an optimal HbA1c a person with type 1 diabetes has to balance between hypoglycaemia and hyperglycaemia when trying to stay in glucose range (4 -10 mmol/L) for as much time of the day and night as possible. Pooling a lot of different studies where both HbA1c and TIR have been measured in various situations and with different techniques, one obtains an approximate linear correlation between HbA1c and TIR (mostly sensor-derived) with lower HbA1c corresponding to more time in range and for a 10%-unit change in TIR there is an 8-9 mmol/mol change in HbA1c (Vigersky and McMahon, 2019).

More data regarding the effects of AHCL systems on HbA1c, and in patients with different baseline levels of HbA1c, seem strongly warranted.

Effects of AHCL on the sensor-derived glucose measures time in range (TIR) and time below range (TBR)

In the only study comparing ACHL to MDI there was a 30%-unit increase in TIR. For the comparison AHCL versus SAP, there was an increase in TIR from approximately 60% to 70%. The key clinical issue is whether this improvement is sufficient to reduce long-term clinical consequences of type 1 diabetes. There are studies associating TIR to diabetes micro-vascular complications in both type 1 and type 2 diabetes (Bellido et al., 2021, Advani, 2020, Raj et al., 2022). A study using capillary glucose derived TIR indicated a 40 to 60% higher risk for diabetic retinopathy and microalbuminuria with a 10%-unit lower TIR (Beck et al., 2019). The association between sensor derived TIR and microvascular complication has so far been shown in short longitudinal or cross-sectional studies (Ranjan et al., 2020, El Malahi et al., 2022). However, the effect is mainly seen in patients with a strongly elevated HbA1c at baseline (fig 17).

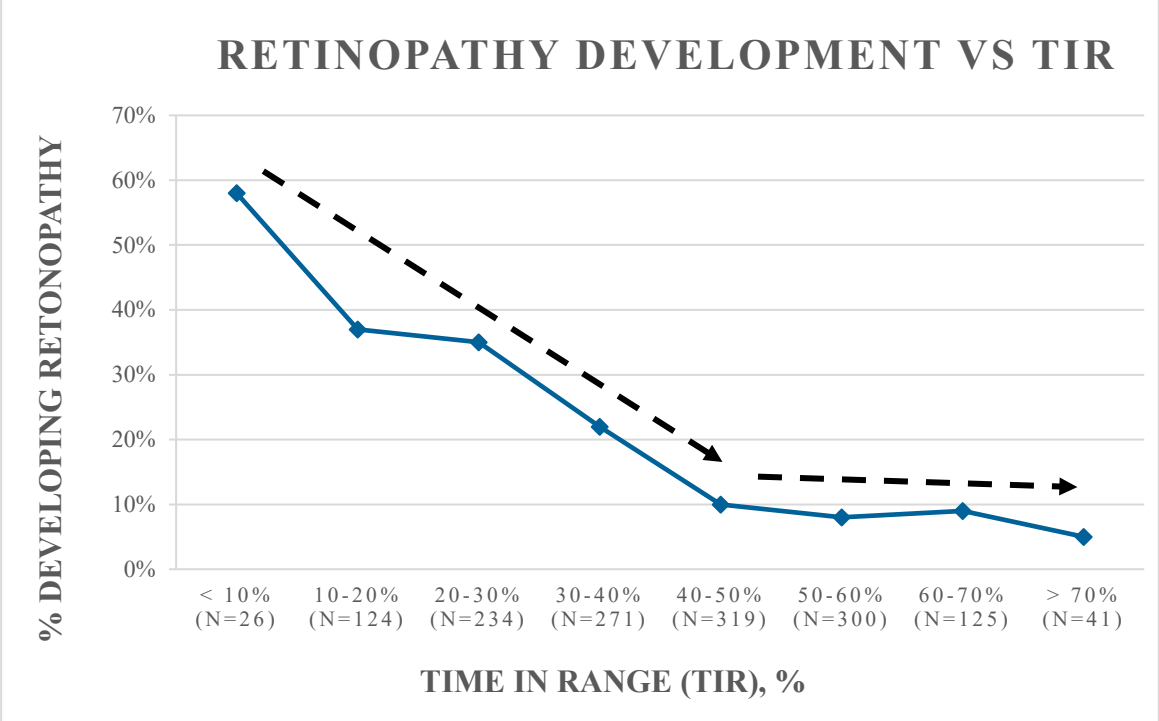


Fig 17 a: Risk of retinopathy development related to % time in range (TIR%) of tissue glucose concentrations. The dashed line indicates the slope of the curve, with a steeper slope for poorly controlled patients with low TIR values. Data from Beck et al., 2019.

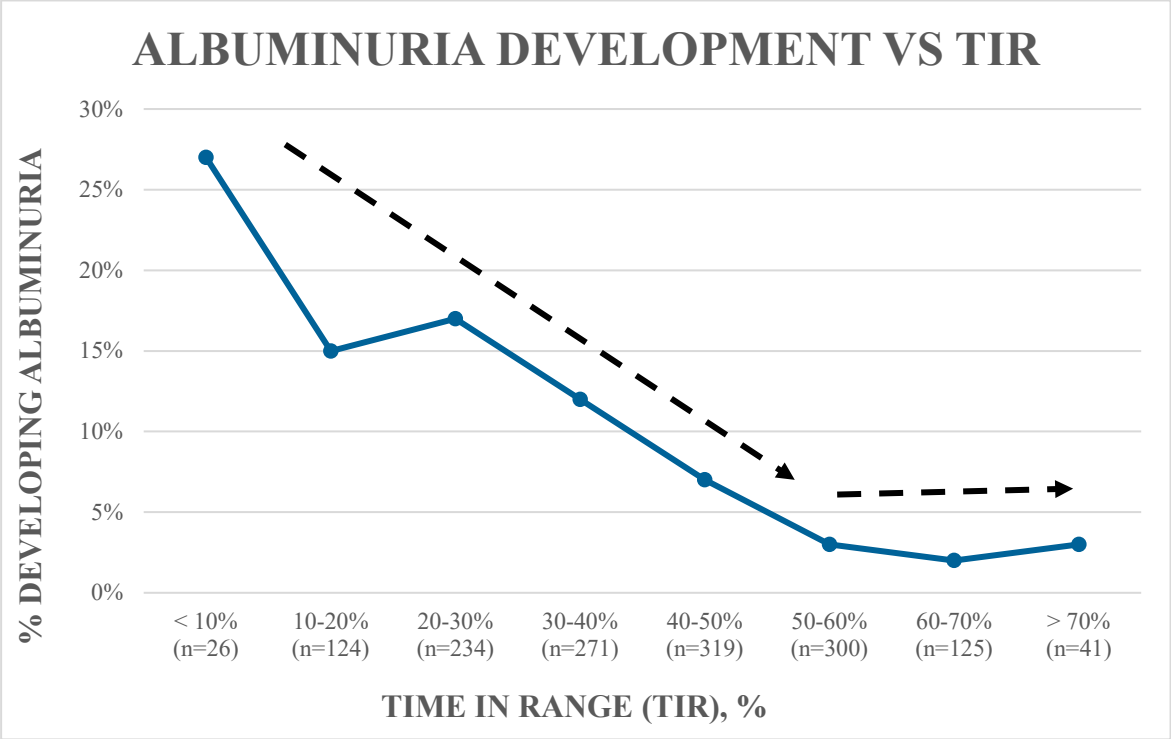


Fig 17 b: Risk of albuminuria development related to % time in range (TIR%) of tissue glucose concentrations. The dashed line indicates the slope of the curve, with a steeper slope for poorly controlled patients with low TIR values. Data from Beck et al., 2019.

Quality of life and patient reported outcome

The included studies in this report showed no consistent difference in patient reported outcomes and the data regarding health-related quality of life was weak. There was however a small increase in treatment satisfaction and somewhat less hypoglycaemia fear in the MDI versus AHCL comparison.

From clinical experience patients starting on AHCL can achieve markedly higher TIR during the night with the support of an automated basal insulin algorithm and often report improved sleep quality. Sleep is important for quality of life but none of the included studies assessed this outcome. However, a study including mixed ages (children, adolescents, and adults) comparing AHCL to SAP with predicted low glucose suspend showed increased treatment satisfaction and improved subjective sleep quality (Wheeler et al., 2022).

Adverse events

There were only a few events of severe hypoglycaemia, ketoacidosis, or other serious adverse events in the included studies on AHCL versus SAP or MDI+sensor. It was therefore not possible to draw any conclusions regarding comparison of risk of serious adverse events.

There were more non-serious adverse events, in particular device issues, with the AHCL system. This was more obvious with the comparison with MDI+sensor, since the AHCL system includes pump, sensor and in some cases also a mobile phone. In Choudhary et al. (2022) only 17 of the non-serious adverse events in the AHCL-group were considered by the authors to be possibly or causally related to the study or device. The corresponding number for the MDI+sensor group were 4 of 39. The two serious adverse events were not considered to be related to the device. The number of participants with adverse events was not reported so it is possible that one person experienced several adverse events. One of the most important reasons for device issues might be that AHCL is a relatively new system, i.e. many participants lacked experience.

For the comparison with SAP there was more adverse events reported with AHCL, but the majority were non-serious and some of the events were clearly not related to the device, such as viral infection and surgery.

Agreements and disagreements with other studies and reviews

There are several studies and reviews which compare AHCL with SAP or a more traditional insulin pump, but several of these studies/reviews have a mixed age population where results are not separately stated for adults. Closed loop system without an autocorrection bolus are in several studies/reviews considered as an AHCL system. A large study with real-world data from 1363 adults with type 1 diabetes, using the ACHL system Tandem t:slim X2 Control-IQ, presented results similar to ours regarding the surrogate measurements time in range, time below range, time above range, and glucose variability (Pinsker et al., 2021b). However, in Pinsker et al. (2021b), time in range was higher, time below and above range lower, and glucose variability lower compared to the results in this report.

Implications for research

In line with the suggested increased improvement regarding time in/below/above range, more studies on long-term complications and the relationship to these variables are needed. We do know that there is a strong relationship between HbA1c and long-term complications. More studies on the effects of AHCL systems on HbA1c and clinical variables are warranted.

14. Future perspectives

Scientific knowledge gaps

The most important knowledge gap is lack of information of the clinical value of the AHCL systems resulting inconsistent but quantitatively modest effect on glucose-related variables also results in reduced long-term diabetic complications. Regarding, AHCL versus manual insulin injections, we only identified one randomized study with some quality issues which was performed in adults with poorly controlled type 1 diabetes. There is a large difference in cost between these two treatments and since MDI with insulin is often the standard treatment for adults with type 1 diabetes today, more studies with good quality are needed.

Use of the AHCL system was associated with a substantial improvement of glucose-related variables but these results need to be confirmed in a prospective interventional RCT with parallel design. For the important surrogate variable HbA1c we found few and to some extent inconsistent studies making the magnitude of the effect hard to evaluate. Also, the Quality of life/patient satisfaction data is inconsistent and hard to evaluate in quantitative terms and for some variables did not reveal any significant improvement with AHCL versus open-loop systems. Data on sleep quality was lacking. This issue also needs to be clarified.

As yet, the AHCL systems have problems handling severe exercise and meals, in these situations the carrier still has to take responsibility for insulin dosage. There is currently a rapid technical development of the systems and also these issues may be possible to handle automatically in the future.

Ongoing research

The search in Clinicaltrials.gov and WHO International Clinical Trials Registry Platform database 01 Dec 2022 identified a total of 802 ongoing trials. However, only three of these studies agreed with our PICO.

The most common reason for wrong population (P) was a inclusion of children in the studied population and lack of clarity regarding handling of the adult population. The most common problems regarding the intervention (I) were use of a system lacking the bolus autocorrection

function, too short an observation period and too few patients in case series. The problem with the comparator (C) was usually wrong comparator and for O the outcomes assessed not being included in our PICO.

Among the three included studies, two were using the Tandem t:slim X2 system (https://clinicaltrials.gov/ct2/show/NCT04266379, https://clinicaltrials.gov/ct2/show/NCT04503174) and one the 780G system (https://clinicaltrials.gov/ct2/show/NCT04520971). Two studies were RCTs with parallel design, with 72 patients (Tandem system) and 95 patients (MiniMed 780 G system). The former was based on hypoglycaemia-prone patients and the latter was a pregnancy study. The other Tandem study was a large case series with 2063 patients in 3 subgroups but the expected number in our specific adult population is not stated. Outcomes are glycaemic variables, HbA1c, severe hypoglycaemia, ketoacidosis and patient satisfaction.

15. Concluding remarks

The assessed literature reports that modern AHCL systems are able to further improve glycaemic control in adult type 1 diabetes patients. Whether the magnitude of the effect is sufficient to reduce risk for angiopathy seems likely but remains to be shown. There were very few emergency or severe adverse events in all groups studied, making a quantitative comparison impossible. This aspect needs to be further closely followed. There are also still some handling issues associated with the new systems, the usability scores do not demonstrate any consistent added value. The data regarding patient-reported outcomes was ambivalent and does not allow any definite conclusions. The cost-effectiveness analysis, based on assumed HbA1c reductions by these new systems, mainly observed in observational studies, are of less value even though indicating acceptable costs per QALY and cost-effectiveness.

Finally it should be remembered that many patients with type 1 diabetes are already well controlled and satisfied with treatment with a sensor and multiple daily injections with insulin, and may not even improve their already excellent glycemic values with an AHCL system. It seems likely that there will be a slow transition towards AHCL systems that may well be accompanied by substantial price reductions.

16. Participants in the project

The question was nominated by
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Patient representative
Leif Sundberg, President of the Diabetic Association in Gothenburg

Declaration of interests
Among authors: CH, CHV, HS, IS, JK, KEO, MP, PS, TS declare no conflict of interest.

Any published statement herein does not automatically imply a conflict of interest but contributes to transparency. All individual declarations of interests have been evaluated by HTA-centrum if there is any relevant association with the present HTA topic.

Project time
The HTA was accomplished during the period of 5 May 2022 – 22 June 2023.
Literature searches were made on 6 May 2022, with an update on 1 December 2022.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue: Does the use of advanced hybrid closed loop insulin pump system, compared with multiple daily injections with sensor based continuous glucose monitoring or a more traditional insulin pump (sensor augmented pump or separate pump and sensor), improve blood glucose control and quality of life and reduce the risk of diabetes complications in adults with type 1 diabetes, without compromising safety?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P
Adults over 18 years of age with type 1 diabetes
I
Insulin delivery system with advanced hybrid closed loop (AHCL) defined as follows:
-Automatically reduces, increases or stops basal insulin
-Automatically provides insulin correction bolus at higher blood glucose
-Patients still need to manually give meal boluses,
Used for at least 2 weeks in daily life*, with 24 hours use
Commercially available systems only, early do-it-yourself systems are excluded
C1
Manual insulin administration via multiple daily injections (MDI) combined with sensor based continuous glucose monitoring
C2
Insulin administration via insulin pump with integrated or separate sensor based continuous glucose monitoring with the following characteristics:
-Cannot automatically increase or decrease basal insulin supply
-Cannot automatically give insulin correction bolus at higher blood glucose
- Patients still need to manually give meal boluses
Pumps with the ability to automatically stop basal insulin at low glucose levels (predictive low glucose suspend) to avoid hypoglycaemia are included
O:
Critical for decision-making
Mortality
Angiopathy:
-Macroangiopathy (ischemic heart disease, stroke, claudication)
-Microangiopathy (retinopathy, nephropathy, neuropathy)
Emergency events:
-Events of diabetic ketoacidosis
-Events of severe hypoglycaemia
HbA1c (an overall measure of glycaemic control)
Health-related quality of life measured with validated instruments

Important for decision-making
Sensor related glucose control:
-Time in range (TIR)
-Time below range (TBR) (Hypoglycaemia)
-Time above range (TAR) (Hyperglycaemia)
- Glucose variability
Patient reported outcomes with validated instruments, ex:
- Sleep
- Depression
- Distress
- Hypoglycaemia fear
- Satisfaction

Adverse events (ex. Insulin administration related complications)

Eligibility critria

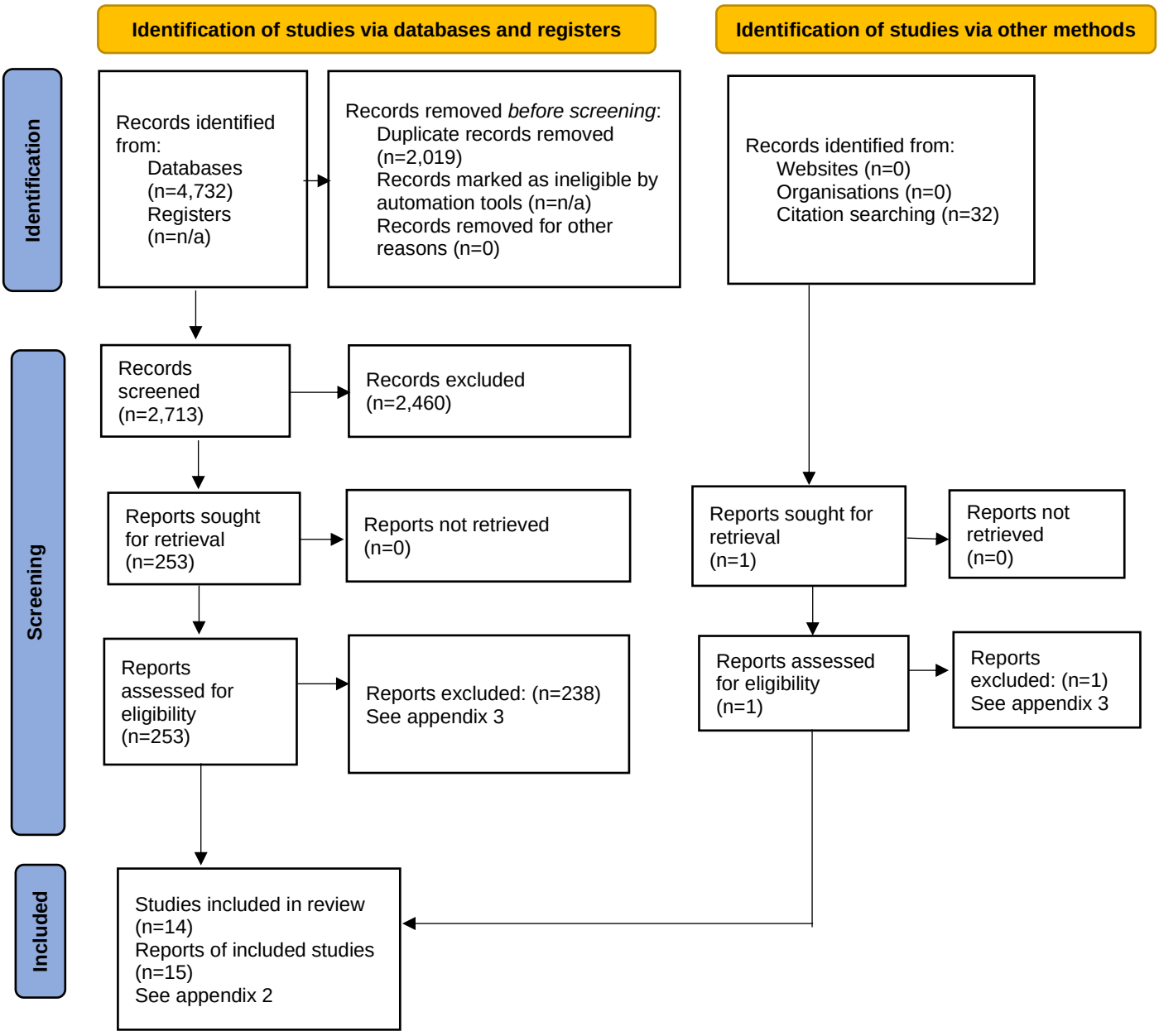
Study design:
RCT, observational studies with control group (n>10 in each group), case series (n>10)

Language:
English, Swedish, Norwegian, Danish

Publication date: 2015-

Selection process – flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



From: Page MJ et al, 2021

Search strategies
Database: Ovid MEDLINE(R) ALL (OvidSP)
Date: 06 May 2022
No. of results: 1,593
Search updated: 01 Dec 2022, 199 results

#	Searches	Results
1	exp Diabetes Mellitus, Type 1/	83038
2	(diabet* or DM1 or DM 1).ab,kf,ti.	725303
3	1 or 2	733131
4	exp Pancreas, Artificial/	972
5	(artificial pancreas or bionic pancreas or automated pancreas or closed loop or closedloop or sensor-augment* or (((continuous adj2 glucose adj2 monitor*) or CGM or rtCGM) adj3 (integr* or automat*)) or ((automat* or integrat*) adj2 insulin adj2 (deliver* or infus* or pump*)) or Medtronics or MiniMed or Omnipod or (Tandem adj1 (slim or IQ or pump*)) or (Dana adj1 (RS or pump*))).ab,kf,ti.	13843
6	4 or 5	14092
7	3 and 6	2945
8	animals/ not (animals/ and humans/)	4970604
9	7 not 8	2786
10	**limit 9 to (yr="2015 -Current" and (danish or english or norwegian or swedish))**	**1593**

Database: Embase 1974 to 2022 May 05 (OvidSP)
Date: 06 May 2022
No. of results: 1,649
Search updated: 01 Dec 2022, 204 results

#	Searches	Results
1	exp insulin dependent diabetes mellitus/	128659
2	(diabet* or DM1 or DM 1).ab,kf,ti.	1083116
3	1 or 2	1098763
4	exp artificial pancreas/	2668
5	exp "glucose monitoring/insulin pump system"/	56
6	(artificial pancreas or bionic pancreas or automated pancreas or closed loop or closedloop or sensor-augment* or (((continuous adj2 glucose adj2 monitor*) or CGM or rtCGM) adj3 (integr* or automat*)) or ((automat* or integrat*) adj2 insulin adj2 (deliver* or infus* or pump*)) or Medtronics or MiniMed or Omnipod or (Tandem adj1 (slim or IQ or pump*)) or (Dana adj1 (RS or pump*))).ab,kf,ti.	18778
7	4 or 5 or 6	19623
8	3 and 7	5491
9	animal/ not (animal/ and human/)	1152383
10	8 not 9	5462
11	limit 10 to ((danish or english or norwegian or swedish) and yr="2015 -Current" and (article or article in press or conference paper or note or "review"))	1667
12	**limit 11 to (embase or medline)**	**1649**

Database: The Cochrane Library
Date: 06 May 2022
No of results: 1,013 ref
Cochrane reviews: 128
Cochrane protocols: 0
Trials: 885
Editorials: 0
Special collections: 0
Clinical answers: 0
Search updated: 01 Dec 2022, 74 results
Cochrane reviews: 10
Trials: 64

ID	Search	Hits
#1	MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees	6017
#2	(diabet* or DM1 or DM 1):ti,ab,kw (Word variations have been searched)	110001
#3	#1 OR #2	110002
#4	MeSH descriptor: [Pancreas, Artificial] explode all trees	82
#5	(((artificial NEXT pancreas) or (bionic NEXT pancreas) or (automated NEXT pancreas) or (closed NEXT loop) or closedloop or (sensor NEXT augment*) or (((continuous NEAR/2 glucose NEAR/2 monitor*) or CGM or rtCGM) NEAR/3 (integr* or automat*)) or ((automat* or integrat*) NEAR/2 insulin NEAR/2 (deliver* or infus* or pump*)) or Medtronics or MiniMed or Omnipod or (Tandem NEAR/1 (slim or IQ or pump*)) or (Dana NEAR/1 (RS or pump*)))):ti,ab,kw (Word variations have been searched)	55379
#6	#4 OR #5	55379
#7	#3 AND #6	4031
#8	(clinicaltrials OR trialsearch):so	398994
#9	#7 NOT #8	2920
#10	(conference abstract):pt	191904
#11	#9 NOT #10	2031
Limit Reviews to publication year 2017-		**128**
Limit Trials to publication year 2015-		**885**

The web-sites of **Statens beredning för medicinsk och social utvärdering (SBU)** and **Folkehelseinstituttet** were visited
06 May 2022
Nothing relevant to the question at issue was found

Search terms used: diabetes, insulin, insulinpump/insulinpumpe, closed loop, closedloop, bukspottkörtel/bukspyttkjertel, bukspottkörtelsystem/bukspyttkjertelsystem, pancreas, pankreas

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Reference lists
A comprehensive review of reference lists brought 32 new records.

Reference lists

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Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1

Appendix 2 - Characteristics of included studies

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Length of follow-up	Study groups: Intervention vs controls	Patients (n)	Mean age years (SD)	Men (%)	Outcome variables
Advanced hybrid closed loop vs multiple daily injections with insulin and sensor							
Choudhary 2022 France Germany UK ADAPT	RCT with parallel design	6 months	AHCL: MiniMed 670G with AHCL algorithm, Guardian 3 sensor vs Multiple daily injections of insulin, isCGM	82	I: 41.5 (11.63) C: 39.7 (13.12)	I: 46% C: 61%	Emergency events HbA1c Quality of life Time in range Time below range Time above range Glucose variability Patient reported outcomes Adverse events
Advanced hybrid closed loop vs SAP with/without PLGS							
RCT							
Anderson 2019a US	RCT with parallel design	4 weeks	AHCL: DiAs/inControl, Roche Accu-Chek Spirit Combo insulin pump, Dexcom G4 sensor vs SAP: Personal insulin pump, Dexcom G4 sensor	47	37 (2)	43	Emergency events Time in range Time below range Time above range Glucose variability Adverse events
Benhamou 2019 France	RCT with cross-over design	12 + 12 weeks 8 weeks washout	AHCL: DBLG1, Cellnovo insulin patch-pump/Kaleido insulin patch-pump, Dexcom G5 sensor vs SAP: personal pump, Dexcom G5 sensor	68	48.2 (13.4)	38	Emergency events HbA1c Time in range Time below range Time above range Glucose variability Patient reported outcomes Adverse events
Collyns 2021 New Zealand	RCT with cross-over design	4+4 weeks 2 weeks washout	AHCL: MiniMed 670G with AHCL algorithm, Guardian sensor vs SAP+PLGM	26 adults	22-80 years No mean	NA for adults	Emergency events Time in range Time below range Time above range

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1

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Author year country	Study design	Length of follow-up	Study groups: Intervention vs controls	Patients (n)	Mean age years (SD)	Men (%)	Outcome variables
Isganaitis 2021 US	RCT with parallel design Secondary analysis of Brown 2019	26 weeks	AHCL: Tandem t:slim X2 Control IQ insulin pump, Dexcom G6 sensor vs SAP: personal pump or Tandem t:slim X2 insulin pump, Dexcom G6 sensor	15 adults	18-24 years No mean	NA for adults	Emergency events HbA1c Time in range Time below range Time above range Glucose variability
Kovatchev 2020a US	RCT with parallel design	13 weeks	AHCL: InControlAP software, Accu-Check Spirit Combo insulin pump, Dexcom G4 sensor vs SAP	82 adults	>25 years No mean	NA for adults	Time below range Time above range
Kovatchev 2020b US	RCT with cross-over design	6 months	AHCL: DiAs, Roche Accu-Check Spirit Combo insulin pump, Dexcom G4 sensor or AHCL: Tandem t:slim X2 Control IQ insulin pump, Dexcom G6 sensor vs SAP	93	45	29	Time in range Time below range Time above range Glucose variability Adverse events
Kudva 2021 US iDCL trial	RCT with parallel design	6 months	AHCL: Tandem t:slim X2 Control IQ insulin pump, Dexcom G6 sensor vs SAP: Insulin pump without PLGS, Dexcom G6 sensor	120 adults	18-71 years No mean	NA for adults	Patient reported outcomes
O`Malley 2021 US iDCL trial	RCT with parallel design Secondary analysis	6 months	AHCL: Tandem t:slim X2 Control-IQ insulin pump, Dexcom G6 sensor vs SAP	105 adults	25-71 years No mean	NA for adults	Time in range
Wheeler 2022 New Zealand	RCT with cross-over design	4+4 weeks 2 weeks washout	AHCL: MiniMed 670 insulin pump with auto correction bolus vs SAP+PLGM	29 adults	18-65 years No mean	NA for adults	Patient reported outcomes

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1

Appendix 2 - Characteristics of included studies

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Author year country	Study design	Length of follow-up	Study groups: Intervention vs controls	Patients (n)	Mean age years (SD)	Men (%)	Outcome variables
Non-randomised studies							
Anderson 2016 US	Non-randomised study (before/after)	2+2 weeks 2 weeks washout	AHCL: DiAs (a smartphone medical platform) Dexcom G4 sensor, Roche Accu-Chek insulin pump, modular CLC algorithm vs SAP	30	44 (18-66 years)	57	Emergency events Time in range Time below range Time above range Glucose variability Adverse events
Bisio 2021 US	Non-randomised study (before/after)	4+4 weeks	AHCL: Tandem t:slim X2 Control-IQ insulin pump, Dexcom G6 sensor vs SAP	18	68.7 (3.3)	60	Emergency events HbA1c Time in range Time below range Time above range Glucose variability Patient reported outcomes Adverse events
Boscari 2022 Italy	Retrospective non-randomised study (before/after)	3 months	AHLC: Tandem t:slim X2 Control-IQ insulin pump vs SAP: Tandem t:slim X2 Basal-IQ insulin pump	31	38 (31-45) Median (IQR)	55	Emergency events HbA1c Time in range Time below range Time above range Glucose variation Patient reported outcomes
Kovatchev 2017 Italy US	Non-randomised study (before/after) Extension (phase 2) of Anderson 2016 Compares to baseline data from phase 1 (Andersson 2016)	5 months	AHCL: DiAs, Roche Accu-Check Spirit Combo insulin pump, Dexcom G4 sensor	14	45	71	Emergency events HbA1c Time in range Time below range Time above range Adverse events
Toschi 2022 US	Retrospective non-randomised study Brief report (before/after)	3 months	AHCL: Tandem t:slim X2 Control-IQ insulin pump vs Pre-AHCL	48	70 (4)	NA for adults	Time in range Time below range Time above range Glucose variability

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1

Appendix 2 - Characteristics of included studies

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Length of follow-up	Study groups: Intervention vs controls	Patients (n)	Mean age years (SD)	Men (%)	Outcome variables

ADAPT: the Advanced Hybrid Closed Loop Study in Adult Population with Type 1 Diabetes, AHLC: advanced hybrid closed loop, C: comparison, CGM: continuous glucose monitoring, CLC: closed-loop control, DBLG1: The Diabeloop Generation 1, DiAs: the Diabetes Advisory System/the Diabetes Assistant (a smartphone medical platform with USS Virginia CLC algorithm), HbA1c: haemoglobin A1c, I: intervention, iDCL trial: the International Diabetes Closed Loop trial, isCGM: intermittent scanning continuous glucose monitoring, IQR: interquartile range, NA: not applicable, PLGM: predictive low glucose management, PLGS: predictive low glucose suspend, RCT: randomised controlled trial, SAP: sensor augmented pump, UK: The United Kingdom, US: The United States of America

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Abitbol 2018	Too short observational period
Amadou 2021	Case series <100
Anderson 2019b	Wrong comparison (components of hybrid systems)
Anonymous 2022	Wrong publication type: news
Arrieta 2022	Wrong patient group (below or above 15 years of age)
Asarani 2021	Wrong publication type: narrative review, no meta-analysis, no quality appraisal
Bally 2017	Wrong intervention, no autocorrection of hyperglycaemia
Bally 2018	Wrong intervention, no autocorrection of hyperglycaemia, and one arm is duplicate to Bally 2017
Barnard 2015	Wrong intervention: not AHCL (no automatic bolus)
Barnard 2017	Wrong intervention: not AHCL (no automatic bolus)
Bashir 2022	Mixed intervention: majority of patients with older closed loop pump without auto correction of hyperglycaemia (MiniMed 670), too few patients with AHCL pump
Bassi 2021	No data for adults only
Beato-Vibora 2021a	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Beato-Vibora 2021b	Wrong patient group (15-65 years)
Beato-Vibora 2021c	Wrong patient group (15-65 years)
Beck 2022	Wrong focus: evaluate insulin sort, still experimental, lack of clarity regarding auto-correction bolus
Bekiari 2018	Mixed intervention: results combined with all kinds of pumps; mixed population: adults, adolescents and children combined
Benhamou 2021	Case series <100
Benhamou 2022	Case series <100
Berg 2018	Wrong intervention: all types of insulin pumps
Bergenstal 2021	Wrong patient group (14-29 years)
Biester 2019	Wrong population: a majority of patients under 18 years, no results per age group
Biester 2021	Wrong intervention: tubeless Omnipod without hybrid closed loop
Bionic Pancreas Research Group 2022	Wrong patient group (mixed ages) and outcomes not presented separately for adults
Blauw 2016	Wrong intervention: dual hormone AP
Blauw 2021	Wrong intervention: dual hormone AP
Boughton 2019	Wrong population: not diabetes
Boughton 2021	Wrong intervention: no automatic correction bolus (CamAPS)
Boughton 2022a	Wrong intervention: no automatic correction bolus (CamAPS)
Boughton 2022b	Wrong intervention: no automatic correction bolus (CamAPS), duplicate of Boughton 2022a
Breton 2018	Wrong intervention and comparison (decision support system)
Breton 2021	Mixed patient population (ages, type 1 and 2 diabetes)
Brogi 2017	Wrong intervention: closed loop systems in general (not only insulin pumps), wrong study design: SR
Brown RE 2021	Wrong intervention: tubeless Omnipod without hybrid closed loop
Brown SA 2015	Case series <100
Brown SA 2017	Too short observational period

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Brown SA 2019	Unclear presentation of results for correct age group in a subgroup analysis in Supplementary Appendix
Brown SA 2020	Wrong patient group (15-65 years)
Brown SA 2021	Wrong patient group (> 14 years)
Buckingham 2018a	Too short observational period
Buckingham 2018b	Wrong intervention (investigational algorithm)
Burnside 2022a	Wrong publication type: abstract
Burnside 2022b	Wrong patient group (include teenagers), wrong intervention (OpenAPS, do-it-yourself)
Calles-Escandon 2018	Wrong intervention (no hybrid system)
Cameron 2017	Wrong intervention (investigational algorithm)
Carlson 2022	Wrong intervention (only automatic basal)
Castellanos 2021	Wrong intervention (addition of glucagon)
Castle 2018	Too short observational period
Charleer 2018	Wrong intervention: SAP
Choudhary 2016	Wrong publication type: commentary
Christiansen 2021	Wrong intervention (investigational system)
Coronel-Restrepo 2020	Duplicate: same publication as Coronel-Restrepo 2021, but published in Spanish edition
Coronel-Restrepo 2021	Wrong intervention: SAP
da Silva 2022	Wrong patient group (patient characteristics not stated)
Dai 2018	Wrong study design: SR
Danne 2018	Wrong population: children; wrong intervention: tubeless Omnipod without hybrid closed loop
Dassau 2015	Wrong comparison (algorithms)
Dassau 2017a	Wrong intervention (new algorithm evaluation)
Dassau 2017b	Case series <100
De Bock 2015	Wrong population: both children and adults, no results per age group
De Ridder 2019	Wrong intervention: CGM, no AHCL pumps
Del Favero 2015	Too short observational period
Delageniere 2021	Wrong focus: usability
Deshpande 2020	Case series <100
Dovc 2019	Wrong intervention: not AHCL (no automatic bolus)
Dovc 2020	Too short observational period
Du 2020	Wrong population: a majority of patients have type 2 diabetes
Duran-Valdez 2017	Wrong intervention: no closed loop; wrong focus: insulin timing
Eberle 2021	Mixed interventions: different technologies for pregnant women with diabetes
Eckstein 2021	Wrong study design: SR
Ekhlaspour 2019	Too short observational period (7 days per intervention), wrong intervention: bionic pancreas (only insulin) with optional meal announcement (no counting of carbs needed) and no need for pre-programmed information on insulin
Ekhlaspour 2022a	Wrong patient group (lower age limit 14 years)

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Ekhlaspour 2022b	Wrong patient group (lower age limit 14 years)
El Malahi 2022	Wrong intervention: SAP
Elbarbary 2022	Wrong patient group (include teenagers), wrong focus: fasting during Ramadan
Emami 2017	Wrong intervention: not AHCL (no automatic bolus)
Fang 2022	Wrong study design: SR
Farrington 2017	Wrong intervention, no autocorrection of hyperglycaemia
Farrington 2018	Wrong study design: interviews
Finan 2015	Wrong comparison (algorithm evaluation, investigational)
Forlenza 2017	Wrong patient group (age)
Forlenza 2019	Wrong patient group (age)
Forlenza 2021	Wrong patient group (age)
Franc 2021	Comparison with two physical activities
Garcia-Tirado 2021	Too short observational period
Garcia-Tirado 2022	Wrong intervention (addition of diabetes medicine)
Garza 2020	Wrong study design: qualitative
Gawreki 2021	Wrong intervention: Do-it-yourself system
Gingras 2018	Wrong intervention and comparison (different types of meals)
Gomez 2015	Wrong intervention: SAP; wrong focus: exercise
Gomez 2021	Wrong intervention: older pumps (no AHCL)
Gomez 2022	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Graf 2017	Wrong outcome: hormone levels
Grant 2021	Wrong outcome (insulin oscillation patterns)
Grunberger 2021	Wrong publication type: review with only one database searched
Guilhem 2017	Case series <100
Haidar 2015	Wrong patient group (teens and adults not separated)
Haidar 2016	Manual sensor-based insulin administration
Haidar 2017	Wrong intervention (participants can give manual corrections at any time, insulin administrated by the study staff on recommendation from the computer/system)
Haidar 2020	Wrong intervention (insulin administrated by the study staff on recommendation from the computer/system)
Haidar 2021a	Wrong interventions (only auto-basal)
Haidar 2021b	Wrong intervention (insulin administrated by the study staff on recommendation from the computer/system)
Haidar 2022	Wrong intervention (no automatic correction bolus), Wrong comparison: diabetic medication vs placebo
Hanaire 2020	Too short observational period
Hashemi 2019a	Wrong intervention (dual-hormone system)
Hashemi 2019b	Wrong population: mixed type 1 and type 2 diabetes
Heller 2017	Wrong intervention: older pump (no AHCL)
Henry 2022	Wrong publication type:" Letters to the editor"

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Hidefjäll 2021	Wrong intervention: SAP
Hood 2021	Wrong patient group (teens and adults not separated)
Howsmon 2018	Wrong focus: evaluation of detection (with an algorithm) of insulin infusion site failure
Ilkowitz 2016	Wrong outcome (glucose after meals)
Jayawardene 2017	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Jendle 2017	Wrong intervention: SAP
Jendle 2021	Wrong study type (modelling study, with attempts to predict the complications expected on the basis of the data in Collyns 2021 and Charleer 2020)
Jeyaventhan 2021	Wrong intervention (only auto-basal or "do-it-yourself")
Jiao X 2022	Wrong patient group (teens and adults not separated in the meta-analysis)
Jiao Y 2022	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Kamusheva 2021	Systematic review of systematic reviews, mixed P and I
Kaur 2022a	Wrong intervention, no autocorrection of hyperglycaemia
Kaur 2022b	Wrong intervention: CGM
Kietaibl 2022	Wrong intervention: all types of insulin pumps
Kjölhede 2021	Wrong intervention: all types of insulin pumps
Knoll 2022	Wrong interventions (SR with mixed closed loop systems included MiniMed 670)
Kropff 2015	Wrong intervention (no autocorrection of hypoglycaemia)
Kropff 2017	Wrong intervention (no autocorrection of hypoglycaemia)
Kruger 2022	Wrong focus: evaluate insulin sort, still experimental, lack of clarity regarding auto-correction bolus
Lambadiari 2022	Wrong outcome (cost, quality-adjusted life expectancy)
Lason 2021	Wrong intervention: older pumps (no AHCL)
Lee 2020	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Lee 2021	Case series <100
Leelarathna 2017a	Wrong intervention: pumps not specified
Leelarathna 2017b	Wrong type of study: letter to the editor)
Leelarathna 2020a	Wrong focus: evaluation of a CGM index
Leelarathna 2020b	Wrong outcome (no original data, e-letter-observations)
Lehmann 2020	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Levy 2022	Wrong patient group (teens and adults not separated), and compares glucose through different parts of the menstruation cycle
Lewis 2016	Wrong publication type: letter
Lin 2022	Wrong focus: beliefs around hypoglycaemia
Longo 2020	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670); wrong focus: lockdown COVID-19
Lum 2021	Wrong intervention (Do-it-yourself)
Lunati 2022	Mixed intervention: results combined with different kinds of pumps

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Ly 2015	Wrong patient group (teens and adults not separated), wrong intervention (only auto-basal, no autocorrection bolus)
Lynch 2022	Case series <100
Major 2020	Wrong population: a majority of patients under 18 years, no results per age group
Matsuoka 2018	Wrong intervention: SAP
McAuley 2021	Wrong intervention: pump without closed loop
McAuley 2022	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Melmer 2019	Wrong intervention (Do-it-yourself)
Messer 2018	Wrong intervention: CGM; wrong publication type: qualitative metasynthesis
Messer 2021	Wrong population: a majority of patients under 18 years, no results per age group
Messori 2017	Wrong intervention (only auto-basal)
Moreno-Fernandez 2019	Wrong intervention: all types of insulin pumps
Moreno-Fernandez 2022	Wrong population (mixed ages), Wrong intervention (mixed pumps including SAP)
Morrison 2022a	Too short observational period
Morrison 2022b	Wrong intervention: Do-it-yourself
Muller-Korbsch 2022	Wrong publication type: ”Letters to the editor”, Wrong intervention: Do-it-yourself
Napoli 2020	Wrong focus: insulin (not pumps)
Nicolucci 2018	Wrong intervention: SAP
Nimri 2017	Wrong population: a majority of patients under 18 years, no results per age group
Nimri 2020	Wrong intervention: AI decision support system
Noor 2022	Wrong intervention: include Medtronic 670 without autocorrection bolus
O´Neal 2022	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Ortolani 2016	Wrong population: children; wrong study design: three case reports; wrong focus: gene mutations
Ostrovski 2020	Wrong focus: dawn phenomenon
Ozaslan 2022a	Too short observational period
Ozaslan 2022b	Duplicate
Pala 2019	Wrong intervention: all types of insulin pumps
Paldus 2019	Too short observational period
Paldus 2021	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Pasqua 2022	Wrong intervention: no autocorrection bolus
Patel 2016	Wrong patient group (teens and adults not separated), wrong focus (if snacks between meals can help avoid lowering of blood glucose during exercise and increase of blood glucose after)
Patel 2022	Wrong intervention (Do-it-yourself)
Pease 2020a	Mixed interventions: different technologies for diabetes type 1
Pease 2020b	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Pease 2020c	Wrong outcome (cost, quality of life years)
Pease 2020d	Wrong study design: SR
Perkins 2015	Wrong intervention: SAP

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Petrovski 2017	Wrong publication type: letter
Picard 2016	Wrong intervention: SAP
Pinsker 2016	Too short observational period
Pinsker 2018	Too short observational period
Pinsker 2021a	Wrong publication type: case reports
Pinsker 2021b	Case series without outcome adverse/emergency events
Pinsker 2022a	Wrong intervention: open loop
Pinsker 2022b	Wrong intervention, no autocorrection of hyperglycaemia
Polonsky 2016	Wrong intervention: pump without closed loop; wrong study design: survey
Polonsky 2022	Case series without outcome adverse/emergency events
Ranjan 2020	Wrong intervention: SAP
Reddy 2016	Too short observational period
Renard 2016	Wrong intervention, no autocorrection of hyperglycaemia
Rilstone 2021	Wrong intervention: SAP
Rosenlund 2015	Wrong intervention: SAP
Rossetti 2017	Wrong intervention (manually adjustment of basal rate every 15 minute according to a CL controller), focus on a meal
Roze 2019a	Wrong intervention (no closed loop)
Roze 2019b	Wrong intervention: SAP
Ruan 2017	Wrong outcome (insulin peak and sensitivity)
Ruan 2018	Wrong intervention (only auto-basal)
Russel 2021	< 10 pat/arm
Sharifi 2016	Wrong intervention (only auto-basal)
Sherr 2016	Wrong patient group (teens and adults not separated), wrong intervention (additional use of diabetic medication)
Sherr 2020	Too short observational period
Song 2020	Wrong patient group (teens and adults not separated), wrong intervention (automatic meal-bolus after meal)
Soupal 2016	Wrong intervention: SAP
Soupal 2020	Wrong intervention: SAP
Spaic 2017	Wrong intervention: pump without closed loop
Stewart 2016a	Wrong intervention, no autocorrection of hyperglycaemia
Stewart 2016b	Wrong publication type: editorial commentary
Stewart 2018a	< 10 pat/arm
Stewart 2018b	Wrong outcome: glucose control during labour
Street 2021	Wrong intervention (Do-it-yourself)
Tagougui 2020	Too short observational period
Takagi 2022	Wrong intervention: SAP
Taleb 2016	Too short observational period
Tanenberg 2015	Wrong intervention: SAP

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Tauschmann 2018	Wrong intervention (only auto-basal)
Taylor 2020	Wrong publication type: commentary
Thabit 2015a	Wrong publication type: poster abstract
Thabit 2015b	Wrong patient group (teens and adults not separated), wrong intervention (only auto-basal)
Thabit 2015c	Wrong intervention (only auto-basal)
Thabit 2022	Wrong intervention: no autocorrection bolus (CamAPs), Publication type: Research letter
Thivolet 2022	Mixed patient group (ages)
Thuillier 2018	Wrong intervention: pump without closed loop; wrong focus: preprandial vs postprandial insulin aspart
Triolo 2016	Wrong intervention: SAP
Tschaikner 2020	Wrong focus: single-port device; wrong intervention: prototype testing
Tsoukas 2021	Too short observational period
Turksoy 2018	Wrong intervention (experimental, also suggests number of carbes needed when the patient glucose levels a decreasing during exercise)
Underland 2017	Wrong intervention (additional use of diabetic medication)
Van Meijel 2018	Wrong focus: bolus calculation
Vetrani 2022	Wrong intervention: older closed loop pump without auto correction of hyperglycaemia (MiniMed 670)
Vinals 2021	Wrong comparison (tolerance to hard physical exertion)
Weinzimer 2022a	Wrong patient group (teens and adults not separated)
Weinzimer 2022b	Wrong patient group (teens and adults not separated); doublet of Weinzimer 2022a
Weisman 2017	Wrong interventions (SR with mixed CL-systems included dual hormone)
Weissberg-Benchell 2017	Wring intervention: bihormonal AP
Weissberg-Benchell 2019	Wrong focus: psychometric properties of INSPIRE measures
Wilson 2020	Too short observational period
Wu 2020	Wrong intervention (Do-it-yourself)
Ziegler 2015	Wrong intervention (full hybrid closed loop including meals)

AHCL: advanced hybrid closed loop, AI: artificial intelligence, AP: artificial pancreas, CGM: continuous glucose monitoring, , SAP: sensor augmented pump, SR: systematic reviews

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.1
Outcome variable: Emergency events (Severe hypoglycaemia and diabetic ketoacidosis)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop vs multiple daily injections with insulin and sensor									
Choudhary 2022 France Germany UK	RCT	82	7 I=5 C=2	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0	High-risk population	+	-	-
Advanced hybrid closed loop vs SAP with/without PLGS									
RCT									
Anderson 2019a US	RCT	47	5 I=3 C=2	Severe adverse events: 0	Severe adverse events: 0	High-risk population Assuming this includes severe hypoglycaemia and diabetic ketoacidosis	?	-	-
Benhamou 2019 France	RCT with crossover design	68	None	Severe hypoglycaemia: 5 Diabetic ketoacidosis: 0	Severe hypoglycaemia: 3 Diabetic ketoacidosis: 0	Number of events	+	?	-
Collyns 2021 New Zealand	RCT with crossover design	26	NA for adults (only one, withdrew during run-in phase, in the entire study)	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0		?	?	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.1
Outcome variable: Emergency events (Severe hypoglycaemia and diabetic ketoacidosis)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Isganaitis 2021 US	RCT Secondary analysis of Brown 2019	15	None	Severe hypoglycaemia: 0	Severe hypoglycaemia: 0	No other emergency events were presented for adults only	?	-	-
Kovatchev 2020b Italy US	RCT with crossover design	93	13	Severe hypoglycaemia: 1 Diabetes ketoacidosis: 0	Severe hypoglycaemia: 2 Diabetes ketoacidosis: 0	2 Severe hypoglycaemia during open loop with study pumps	+	?	-
Non-randomised studies									
Anderson 2016 US	Non-randomised study (before/after)	30	None	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0		+	-	-
Bisio 2021 US	Non-randomised study (before/after)	18	3	Adverse events: 0	Adverse events: 0	Assuming this includes severe hypoglycaemia and ketoacidosis	+	-	-
Boscari 2022 Italy	Retrospective non-randomised study (before/after)	31	None	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0		+	-	-
Kovatchev 2017 Italy US	Non-randomised study (before/after) Extension (phase 2) of Anderson 2016 Compares to baseline data from phase 1 (Andersson 2016)	14	1	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0	Severe hypoglycaemia: 0 Diabetic ketoacidosis: 0	Compared to baseline data from phase 1; 2 weeks SAP (Andersson 2016)	?	-	-

AHLC: advanced hybrid closed loop, NA: not applicable, PLGS: predictive low glucose suspend, RCT: randomised controlled trial, SAP: sensor augmented pump, UK: The United Kingdom, US: The United States of America

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.2
Outcome variable: HbA1c

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop vs multiple daily injections with insulin and sensor									
Choudhary 2022 France Germany UK	RCT with parallel design	82	8 I=5 C=3	7.32 (0.61) % <u>Change from baseline</u> -1.54 (0.73) % Model-based treatment effect (95% CI): -1.42 (-1.74 to -1.10) % p<0.0001	8.91 (0.78) % <u>Change from baseline</u> -0.20 (0.80) %	High-risk population 6 months follow-up	+	-	?
Advanced hybrid closed loop vs SAP with/without PLGS									
RCT									
Benhamou 2019 France	RCT with cross-over design	68	5	**Change from baseline:** -0.29 (0.6) % Paired difference (95% CI) -0.15 (-0.33 to 0.03) p=0.098 -3.20 (5.7) mmol/mol Paired difference (95% CI) -1.63 (-3.57 to 0.31) p=0.098	**Change from baseline:** -0.14 (0.6) % -1.57 (5.6) mmol/mol	12 weeks follow-up	+	?	?
Isganaitis 2021 US	RCT with parallel design Secondary analysis of Brown 2019	15	None	7.32 (0.55) % Mean difference: 0.14 (95% CI -0.96 to 1.24)	7.18 (1.30) %	Mean difference calculated from data 26 weeks follow-up	?	-	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.2
Outcome variable: HbA1c

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Non-randomised studies									
Bisio 2021 US	Non-randomised study (before/after)	18	3	6.7 (0.5) % p=0.122	7.0 (0.8) %	HbA1c did not change from baseline in either group 4 weeks follow-up	+	-	-
Boscari 2022 Italy	Retrospective non-randomised study (before/after)	31	4	6.6 (0.5) % Mean of the differences (95% CI) 0.4 (-0.6 to -0.2) p<0.0001 48.4 (5.1) mmol/mol Mean of the differences (95% CI) 4.8 (-6.9 to 2.6) p=0.0001	7.0 (0.5) % 53.2 (5.6) mmol/mol	3 moths follow-up	+	-	?
Kovatchev 2017 Italy US	Non-randomised study (before/after) Extension (phase 2) of Anderson 2016 Compares to baseline data from phase 1 (Andersson 2016)	14	1	7.0 (0.6) % 53 (7) mmol/mol p=0.23	7.2 (0.6) % 55 (7) mmol/mol	Compared to baseline data from phase 1; 2 weeks SAP (Andersson 2016) 5 months follow-up	?	-	-

AHLC: advanced hybrid closed loop, CI: confidence interval, HbA1c: haemoglobin A1c, PLGS: predictive low-glucose management, RCT: randomised controlled trial, SAP: sensor augmented pump, SD: standard deviation, UK: The United Kingdom, US: The United States of America

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGM in adults with diabetes type 1
Appendix 4.3
Outcome variable: Health-related quality of life with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) if not otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections with insulin				
Choudhary 2022 France Germany UK	RCT	82	33-50 I=17-22 C=16-28 (Depending on domain)	**Change in DQoL scores from baseline** <u>Total score</u> 5.9 (10.60) Model-based treatment effect (95% CI) 3.8 (−2.1 to 9.7) p=0.20 <u>Treatment satisfaction score</u> 10.3 (16.35) Model-based treatment effect (95% CI) 12.4 (3.9 to 21.0) p=0.0052 <u>Treatment impact score</u> 4.4 (8.05) Model-based treatment effect (95% CI) 4.0 (−0.2 to 8.3) p=0.062 <u>Social worry score</u> −0.3 (14.78) Model-based treatment effect (95% CI) −2.1 (−11.2 to 7.0) p=0.64	**Change in DQoL scores from baseline** <u>Total score</u> 1.5 (10.08) <u>Treatment satisfaction score</u> −2.7 (13.57) <u>Treatment impact score</u> 0.1 (6.69) <u>Social worry score</u> 2.3 (10.64)	High risk population Mean points Scale total score 0-100 Only data from France and UK were available	+	-	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGM in adults with diabetes type 1
Appendix 4.3
Outcome variable: Health-related quality of life with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) if not otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections with insulin				
				Diabetes worry score 5.4 (15.41) Model-based treatment effect (95% CI) −1.7 (−11.3 to 7.8) p=0.72 General well-being score 6.1 (16.96) Model-based treatment effect (95% CI) 7.2 (−1.4 to 15.8) p=0.10	Diabetes worry score 6.7 (12.99) General well-being score −1.3 (11.96)				

AHCL: advanced hybrid closed loop, CI: confidence interval, DQoL: Diabetes Quality of Life questionnaire, RCT: randomised controlled trial, SD: standard deviation, UK: The United Kingdom

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.4
Outcome variable: Time in range (TIR), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country Trial acronym	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop vs multiple daily injections with insulin and sensor									
Choudhary 2022 France Germany UK	RCT with parallel design	82	15 I=5 C=10	**70–180 mg/dL** 70.6 (9.70) % Model-based treatment effect (95% CI): 27.6 (21.63 to 33.6) % p<0.0001	**70–180 mg/dL** 43.6 (15.37) %	High risk population	+	-	?
Advanced hybrid closed loop vs SAP with/without PLGS									
RCT									
Anderson 2019a US	RCT with parallel design	47	Experimental: 2 Control: 1 CGM data missing: 2	**70-180 mg/dL** 78.2 (10) %	**70-180 mg/dL** 59.6 (16.5) %	High-risk population	?	-	+
Benhamou 2019 France	RCT with cross-over design	68	5 I=3 C=2	**3.9-10.0 mmol/L** 68.5 (9.4) % Paired difference (95% CI) 9.2 (6.4 to 11.9) p<0.0001 **4.4–7.8 mmol/L** 39.3 (7.9) % Paired difference (95% CI) 5.8 (3.7 to 7.9) p<0.0001	**3.9-10.0 mmol/L** 59.4 (10.2) % **4.4–7.8 mmol/L** 33.5 (7.9) %		+	?	+

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.4
Outcome variable: Time in range (TIR), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country Trial acronym	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Collyns 2021 New Zealand	RCT with cross-over design	26	NA for adults (only one, withdrew during run-in phase, in the entire study)	**3.9–10.0 mmol/L** 73.9 (8.2) % CGM absolute difference: 11.9 (9.5) % p<0.0001	No data		?	?	?
Isganaitis 2021 US	RCT with parallel design Secondary analysis	15	None	**70-180 mg/dL** 63 (7) %	**70-180 mg/dL** 55 (14) %		?	-	-
Kovatchev 2020b Italy US	RCT with cross-over design	93	16	**3.9–10mmol/L** 69.5 (10.9) %	**3.9–10mmol/L** 58.6 (14.6) %		+	?	+
O`Malley 2021 US iDCL trial	RCT with parallel design Secondary analysis	105 adults	None	**70–180 mg/dL** Week before parameter change 76.0 (66.0–82.1) Week after parameter change 75.7 (67.8–83.9) Calculated data mean (SD): 75.7 (11.9)	**70–180 mg/dL** Week before parameter change 63.5 (52.1–70.7) Week after parameter change 66.0 (52.9–72.8) Calculated data mean (SD): 66.0 (14.7)	Median (IQR)	?	?	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.4
Outcome variable: Time in range (TIR), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country Trial acronym	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Non-randomised studies									
Anderson 2016 US	Non-randomised study (before/after)	30	1	**70–180 mg/dL** 73 (68, 76) % p=<0.001	**70–180 mg/dL** 65 (59, 69) %	Median (IQR) Could not be calculated to mean/SD	+	-	?
Bisio 2021 US	Non-randomised study (before/after)	18	3	**70–180 mg/dL** 79.6 (7.8) % p=0.002	**70–180 mg/dL** 69.6 (14.2) %		+	-	?
Boscari 2022 Italy	Retrospective non-randomised (before/after)	31	None	**70–180 mg/dL** 74.0 (7.7) % Mean of the differences (95% CI) 11.3 (8.7 to 13.9) p<0.0001 **70–140 mg/dL** 44.6 (8.9) % Mean of the differences (95% CI) 7.5 (5.0 to 10.0) p<0.0001	**70–180 mg/dL** 62.7 (12.0) % **70–140 mg/dL** 37.1 (12.1) %		+	-	?

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.4
Outcome variable: Time in range (TIR), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country Trial acronym	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Kovatchev 2017 Italy US	Non-randomised study (before/after) Extension (phase 2) of Anderson 2016 Compares to baseline data from phase 1 (Andersson 2016)	14	1	**3.9–10 mmol/L** 77 (73-81) % p<0.001	**3.9–10 mmol/L** 66 (59-69) %	Median (IQR) Could not be calculated to mean/SD Compared to baseline data from phase 1; 2 weeks SAP (Andersson 2016)	?	-	?
Toschi 2022 US	Retrospective non-randomised study Brief report (before/after)	48	11	**70–180 mg/dL** 76 (9) % p<0.001	**70–180 mg/dL** 62 (14) %		+	-	?

AHLC: advanced hybrid closed loop, CGM: continuous glucose monitoring, CI: confidence interval, iDCL trial: the International Diabetes Closed Loop trial, IQR: interquartile range, NA: not applicable, PLGS: predictive low glucose suspend, RCT: randomised controlled trial, SAP: sensor augmented pump, SD: standard deviation, UK: The United Kingdom, US: The United States of America

Project: A comparison of advanced hybrid closed loop systems and multiple daily injections with SAP with/without PLGS in adults with diabetes type 1
Appendix 4.5
Outcome variable: Time below range (Hypoglycaemia), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop vs multiple daily injections with insulin and sensor									
Choudhary 2022 France Germany UK	RCT with parallel design	82	15 I=5 C=10	**<70 mg/dL** 2.6 (2.01) % Model-based treatment effect (95% CI): 0.1 (−0.7 to 1.0) Non-inferiority met **<54 mg/dL** 0.6 (0.67) % Model-based treatment effect (95% CI): −0.1 (−0.4 to 0.3) Non-inferiority met	**<70 mg/dL** 2.6 (2.55) % **<54 mg/dL** 0.7 (1.17) %	High-risk population	+	-	?
Advanced hybrid closed loop vs SAP with/without PLGS)									
RCT									
Anderson 2019a US	RCT with parallel design	47	5 I=3 C=2	**<3.9 mmol/l** 2.0 (1.4) % **<3.3 mmol/l** 0.8 (0.7) % **<3.0 mmol/l** 0.3 (0.4) %	**<3.9 mmol/l** 4.8 (4.5) % **<3.3 mmol/l** 2.1 (2.5) % **<3.0 mmol/l** 0.9 (1.1) %	High-risk population	?	-	+

Project: A comparison of advanced hybrid closed loop systems and multiple daily injections with SAP with/without PLGS in adults with diabetes type 1
Appendix 4.5
Outcome variable: Time below range (Hypoglycaemia), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Benhamou 2019 France	RCT with cross-over design	68	5	**<3.9 mmol/l:** 2.0 (2.4) % Paired ratio (95% CI) -2.4 (-3.0 to -1.7) p<0.0001 **<3.3 mmol/l:** 0.8 (0.8) % Paired ratio (95% CI) -1.3 (-1.6 to -0.9) p<0.0001 **<2.8 mmol/l:** 0.2 (0.8) % Paired ratio (95% CI) -0.5 (-0.7 to -0.3) p<0.0001	**<3.9 mmol/l:** 4.3 (2.4) % **<3.3 mmol/l:** 2.0 (1.6) % **<2.8 mmol/l:** 0.7 (0.8) %		+	?	+
Collyns 2021 New Zealand	RCT with cross-over design	26	NA for adults (only one, withdrew during run-in phase, in the entire study)	**<3.9 mmol/L** -0.1±0.9 p=0.5184 **<3.0 mmol/L** -0.0±0.2 p=0.5462	No data	CGM absolute difference	?	?	?
Isganaitis 2021 US	RCT with parallel design Secondary analysis	15	None	**<u><70 mg/dL</u>** 1.6 (1.0) % **<u><54 mg/dL</u>** 0.4 (0.3) %	**<u><70 mg/dL</u>** 2.5 (2.2) % **<u><54 mg/dL</u>** 0.4 (0.5) %		?	-	-

Project: A comparison of advanced hybrid closed loop systems and multiple daily injections with SAP with/without PLGS in adults with diabetes type 1
Appendix 4.5
Outcome variable: Time below range (Hypoglycaemia), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Kovatchev 2020a US	RCT with parallel design	82	NA for adults 2 in the entire group (AHCL:1 and SAP:1)	**<3.9 mmol/L** 2.8 (1.9) % p=0.96	**<3.9 mmol/L** 3.5 (3.4) %	From a table in supplementary appendix	?	?	?
Kovatchev 2020b US	RCT with cross-over design	93	16	**<3.9 mmol/L** 1.8 (1.4) % **<3 mmol/L** 0.41 (0.41) %	**<3.9 mmol/L** 4.0 (3.3) % **<3 mmol/L** 1.11 (1.34) %		+	?	+
Non-randomised studies									
Anderson 2016 US	Non-randomised study (before/after)	30	1	**<70 mg/dL** 1.7 (1.1, 2.7) % p<0.0001	**<70 mg/dL** 4.1 (2.0, 7.8) %	Median (IQR) Could not be calculated to mean/SD	+	-	?
Bisio 2021 US	Non-randomised study (before/after)	18	3	**<70 mg/dL** 0.8 (0.7) % p=0.053 **<54 mg/dL** 0.1 (0.1) % Ns	**<70 mg/dL** 1.2 (2.5) % **<54 mg/dL** 0.1 (0.6) %		+	-	?
Boscari 2022 Italy	Retrospective non-randomised study (before/after)	31	None	**<70 mg/dL** 1.5 (1.3) % Mean of the differences (95% CI) 0.2 (-0.6 to 0.2) p=0.43 **<54 mg/dl** 0.2 (0.4) %	**<70 mg/dL** 1.7 (1.5) % **<54 mg/dl** 0.2 (0.3) %		+	-	?

Project: A comparison of advanced hybrid closed loop systems and multiple daily injections with SAP with/without PLGS in adults with diabetes type 1
Appendix 4.5
Outcome variable: Time below range (Hypoglycaemia), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
				Mean of the differences (95% CI) 0.1 (-0.1 to 0.2) p=0.65					
Kovatchev 2017 Italy US	Non-randomised study (before/after) Extension (phase 2) of Anderson 2016 Compares to baseline data from phase 1 (Andersson 2016)	14	1	**<3.9 mmol/L** 1.3 (0.6-1.7) p<0.001 **<3.3 mmol/L** 0.3 (0.2-0.6) p<0.001 **<2.8 mmol/L** 0.1 (0.0-0.2) p<0.001	**<3.9 mmol/L** 4.1 (2.9-7.5) **<3.3 mmol/L** 2.2 (1.5-3.4) **<2.8 mmol/L** 1.0 (0.8-1.3)	Median (IQR) Could not be calculated to mean/SD Compared to baseline data from phase 1; 2 weeks SAP (Andersson 2016)	?	-	?
Toschi 2022 US	Retrospective non-randomised study Brief report (before/after)	48	11	**<70 mg/dL** 1.0 (1.0, 2.0) % p=0.03 **<54 mg/dL** 0 (0, 0.5) Ns	**<70 mg/dL** 2.0 (1.0, 3.0) % **<54 mg/dL** 0 (0, 0.5)	Median (IQR) Could not be calculated to mean/SD	+	-	?

AHLC: advanced hybrid closed loop, CGM: continuous glucose monitoring, CI: confidence interval, IQR: interquartile range, NA: not applicable, Ns: non-significant, PLGS: predictive low glucose suspend, RCT: randomised controlled trial, SAP: sensor augmented pump, SD: standard deviation, UK: The United Kingdom, US: The United States of America

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.6
Outcome variable: Time above range (Hyperglycaemia), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop with multiple daily injections with insulin and sensor									
Choudhary 2022 France Germany UK	RCT with parallel design	82	15 I=5 C=10	**>180 mg/dL** 26.7 (10.44) % Model-based treatment effect (95% CI): −27.9 (−34.2 to −21.6) p<0.0001 **>250 mg/dL** 6.6 (5.02) % Model-based treatment effect (95% CI): −16.9 (−21.4 to −12.4) p<0.0001	**>180 mg/dL** 53.8 (16.47) % **>250 mg/dL** 22.5 (13.19) %	High-risk population	+	-	?
Advanced hybrid closed loop with SAP with/without PLGS									
RCT									
Anderson 2019a US	RCT with parallel design	47	5 I=3 C=2	**>180 mg/dL** 19.8 (10.1) % **>250 mg/dL** 3.6 (3.9) % **>300 mg/dL** 1.1 (1.8) %	**>180 mg/dL** 35.6 (17.6) % **>250 mg/dL** 11.2 (9.4) % **>300 mg/dL** 3.6 (5.6) %	High-risk population	?	-	?

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.6
Outcome variable: Time above range (Hyperglycaemia), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Benhamou 2019 France	RCT with cross-over design	68	5	**>10.0 mmol/L** 29.5 (10.2) % Paired difference (95% CI) -6.8 (-9.7 to -3.9) p<0.0001 **>13.9 mmol/L** 7.4 (6.3) % Paired difference (95% CI) -4.3 (-6.2 to -2.4) p<0.0001 **>16.7 mmol/L** 2.4 (3.1) % Paired difference (95% CI) -2.0 (-3.0 to -1.0) p=0.0002	**>10.0 mmol/L** 36.3 (10.2) % **>13.9 mmol/L** 11.7 (6.3) % **>16.7 mmol/L** 4.3 (3.1) %		+	?	+
Collyns 2021 New Zealand	RCT with cross-over design	26	NA for adults (only one, withdrew during run-in phase, in the entire study)	**<10.0 mmol/L** -11.8 (10.0) % p<0.0001	No data	CGM absolute difference	?	?	?
Isganaitis 2021 US	RCT with parallel design Secondary analysis of a subgroup	15	None	**>180 mg/dL** 35 (7) % **>250 mg/dL** 9.4 (4.3) %	**>180 mg/dL** 43 (15) % **>250 mg/dL** 15.0 (11.0) %		?	-	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.6
Outcome variable: Time above range (Hyperglycaemia), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
				>300 mg/dL 2.7 (1.8) %	**>300 mg/dL** 5.8 (7.0) %				
Kovatchev 2020a US	RCT with parallel design	82	NA for adults (2 in the entire group)	**<10.0 mmol/L** 30 (10) % p=0.23	**<10.0 mmol/L** 36 (15) %	From a table in supplementary appendix	?	?	?
Kovatchev 2020b Italy US	RCT with cross-over design	93	16	**<10.0 mmol/L** 28.7 (11.4) % **<13.3 mmol/L** 7.3 (5.9) %	**<10.0 mmol/L** 37.4 (16.5) % **<13.3 mmol/L** 12.6 (10.5) %		+	?	+
Non-randomised studies									
Anderson 2016 US	Non-randomised study (before/after)	30	1	**>180 mg/dL** 25 (22, 28) % p=0.001	**>180 mg/dL** 32 (25, 36) %	Median (IQR) Could not be calculated to mean/SD	+	-	?
Bisio 2021 US	Non-randomised study (before/after)	18	3	**>180 mg/dL** 19.3 (8.1) % p=0.05 **>250 mg/dL** 2.56 (3.6) % p=0.001	**>180 mg/dL** 26.6 (15.5) % **>250 mg/dL** 4.18 (7.0) %		+	-	?
Boscari 2022 Italy	Retrospective non-randomised (before/after)	31	None	**>180 mg/dL** 24.4 (8.0) % Mean of the differences (95% CI) -11.2 (-13.8 to -8.5) p<0.0001 **>250 mg/dL** 4.6 (2.6) %	**>180 mg/dL** 35.6 (12.4) % **>250 mg/dL** 8.5 (5.7) %		+	-	?

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.6
Outcome variable: Time above range (Hyperglycaemia), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
				Mean of the differences (95% CI) -4.0 (-5.3 to -2.6) p<0.0001					
Kovatchev 2017 Italy US	Non-randomised study (before/after) Extension (phase 2) of Anderson 2016 Compares to baseline data from phase 1 (Andersson 2016)	14	1	**>10.0 mmol/L** 22 (19-27) p=0.01 **>13.9 mmol/L** 3 (2-6) p=0.006 **>16.7 mmol/L** 0 (0-1) p=0.14	**>10.0 mmol/L** 31 (23-38) **>13.9 mmol/L** 6 (3-11) **>16.7 mmol/L** 2 (0-3)	Median (IQR) Could not be calculated to mean/SD Compared to baseline data from phase 1; 2 weeks SAP (Andersson 2016)	?	-	?
Toschi 2022 US	Retrospective non-randomised study Brief report (before/after)	48	11	**>180 mg/dL** 20 (9) % p<0.001 **>250 mg/dL** 3.2 (3) % Ns	**>180 mg/dL** 30 (11) % **>250 mg/dL** 6 (7) %		+	-	?

AHLC: advanced hybrid closed loop, CGM: continuous glucose monitoring, CI: confidence interval, IQR: interquartile range, NA: not applicable, Ns: non-significant, PLGS: predictive low glucose suspend, RCT: randomised controlled trial, SAP: sensor augmented pump, SD: standard deviation, UK: The United Kingdom, US: The United States of America

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.7
Outcome variable: Glucose variability (Coefficient of variation of sensor glucose values), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop with multiple daily injections with insulin and sensor									
Choudhary 2022 France Germany UK	RCT with parallel design	82	15 I=5 C=10	35.5 (4.46) % Model-based treatment effect (95% CI): 0.6 (-1.4 to 2.5) p=0.57	35.9 (5.74) %	High-risk population	+	-	?
Advanced hybrid closed loop with SAP with/without PLGS									
RCT									
Anderson 2019a US	RCT with parallel design	47	5 I=3 C=2	0.32 (0.04) Mean difference (95% CI) -0.05 (-0.08 to -0.02)	0.37 (0.07)	High-risk population Mean difference calculated from data	?	-	+
Benhamou 2019 France	RCT with cross-over design	68	5	31.0 (3.9) % Paired difference (95% CI) -2.3 (-3.1 to -1.5) p< 0.0001	33.3 (3.9) %		+	?	+
Isganaitis 2021 US	RCT with parallel design Secondary analysis	15	None	35 (3) %	37 (6) %		?	-	-
Kovatchev 2020b Italy US	RCT with cross-over design	93	16	34.3 (4.0) %	37.8 (4.5) %		+	?	+

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.7
Outcome variable: Glucose variability (Coefficient of variation of sensor glucose values), sensor based

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Non-randomised studies									
Anderson 2016 US	Non-randomised study (before/after)	30	1	34 (31, 37) % p<0.001 34 (4.44) %	38 (34, 41) % 38 (5.19) %	Median (IQR) Mean (SD) calculated from data	+	-	?
Bisio 2021 US	Non-randomised study (before/after)	18	3	30.3 (4.8) % p=0.006	33.7 (4.9) %		+	-	?
Boscari 2022 Italy	Retrospective non-randomised (before/after)	31	None	31.8 (4.2) % Mean of the differences (95% CI) 1.5 (-2.6 to 0.5) p=0.004	33.3 (4.4) %		+	-	?
Toschi 2022 US	Retrospective non-randomised study Brief report (before/after)	48	11	29 (8) % p=0.001	35 (6) %		+	-	?

AHLC: advanced hybrid closed loop, CGM: continuous glucose monitoring, CI: confidence interval, IQR: interquartile range, PLGS: predictive low glucose suspend, RCT: randomised controlled trial, SAP: sensor augmented pump, SD: standard deviation, UK: The United Kingdom, US: The United States of America

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.8
Outcome variable: Patient reported outcomes with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop with multiple daily injections with insulin and sensor									
Choudhary 2022 France Germany UK	RCT with parallel design	82	8-9 I=6 C=2-3 (Depending on instrument)	**Diabetes satisfaction treatment questionnaire** DTSQs score Change since baseline: 6.1 (7.55) Model-based treatment Effect (95% CI): 6.2 (2.9 to 9.4) p=0.0003 DTSQc score Change since baseline: 13.7 (4.39) Model-based treatment effect (95% CI): 9.8 (7.04 to 12.64) p<0.0001 **Hypoglycaemia fear survey** Change in total score -10.2 (15.51) Model-based treatment effect (95% CI): -6.9 (-13.5 to -0.3) p=0.041 Change in behaviour subscale	**Diabetes satisfaction treatment questionnaire** DTSQs score Change since baseline: 0.2 (6.84) DTSQc score Change since baseline: 3.7 (7.24) **Hypoglycaemia fear survey** Change in total score -2.7 (13.08)	High-risk population Change since baseline **DTSQs:** (scale 0-36) higher scores are positive **DTSQc:** score -18 to 18, higher positive scores indicate improved treatment satisfaction **HFS-II:** Total score 0–132, higher score indicates greater fear	+	-	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.8
Outcome variable: Patient reported outcomes with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	**Control: multiple daily injections or SAP with/without PLGS**				
				-4.8 (8.73) Model-based treatment effect (95% CI): -3.8 (-7.5 to -0.1) p=0.047 <u>Change in worry subscale</u> -5.4 (10.42) Model-based treatment effect (95% CI): -3.0 (-7.4 to 1.4) p=0.18	<u>Change in behaviour subscale</u> −0.7 (7.52) <u>Change in worry subscale</u> −2.0 (8.58)	<u>Behaviour scale</u> 0–60, higher behaviour scores indicate greater tendency to avoid hypoglycaemia. <u>Worry scale</u> 0–72, higher scores indicate more worry			
Advanced hybrid closed loop with SAP with/without PLGS									
RCT									
Benhamou 2019 France	RCT with cross-over design	68	5	**Diabetes treatment satisfaction questionnaire** Value at visit: 27.2 (7.4) Mean Difference: -0.70 (95% CI -2.91 to 1.51) Change from baseline: 0.2 (8.9) **Visual Analogical Scales** <u>Satisfaction</u> Value at visit: 6.9 (2.9) Mean Difference: 0.20 (-0.70 to 1.10) Change from baseline: 0.0 (4.0)	**Diabetes treatment satisfaction questionnaire** Value at visit: 27.9 (5.0) Change from baseline: 1.0 (5.8) **Visual Analogical Scales** <u>Satisfaction</u> Value at visit: 6.7 (2.2) Change from baseline: 0.0 (2.6)	Mean difference calculated from data **DTSQ:** (scale 0-36) higher scores are positive **VAS:** (scale 0-10) higher scores are positive	+	?	?

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.8
Outcome variable: Patient reported outcomes with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	**Control: multiple daily injections or SAP with/without PLGS**				
				Difficulty of use Value at visit: 6.9 (2.8) Mean Difference: -1.10 (95% -1.92 to -0.28) Change from baseline: -0.6 (3.4) Satisfaction to wear Value at visit: 7.0 (2.3) Mean Difference: 0.8 (95% CI -0.04 to 1.64) Change from baseline: 0.9 (3.4)	Difficulty of use Value at visit: 8.0 (1.8) Change from baseline: 0.5 (2.4) Satisfaction to wear Value at visit: 6.2 (2.5) Change from baseline: 0.0 (3.3)				
Kudva 2021 US iDCL trial	RCT with parallel design Secondary analysis	120	1	**Diabetes Distress Survey** 1.7 (0.6) Mean adjusted treatment difference (95% CI): -0.11 (-0.31 to 0.09) p=0.30 **Hypoglycemia fear survey** 33 (12) Mean adjusted treatment difference (95% CI): -3.1 (-7.8 to 1.6) p=0.23 **INSPIRE survey** 87 (14) Mean adjusted treatment difference (95% CI): 5.1 (-0.6 to 10.9) p=0.09	**Diabetes distress Survey** 1.9 (0.8) **Hypoglycemia fear survey** 38 (18) **INSPIRE survey** 86 (13)	Data from final visit (26 weeks) **DDS:** score 1-6, higher scores indicate more distress **HFS-II:** score 0–132, higher total score indicates greater fear **INSPIRE:** scale 0-100, higher score is positive	?	-	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.8
Outcome variable: Patient reported outcomes with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Wheeler 2022 New Zealand	RCT with cross-over design	29 adults	HFS-II: 1	**Diabetes treatment satisfaction questionnaire** DTSQs 30.9 (0.7) p=0.004 DTSQc 11.7 (0.8) p=0.032 **Hypoglycemia fear survey** Behaviour subscale 1.13 (0.08) p=0.189 Worry subscale 1.01 (0.11) p=0.572	**Diabetes treatment satisfaction questionnaire** DTSQs 27.9 (0.7) DTSQc 9.2 (0.9) **Hypoglycemia fear survey** Behaviour subscale 1.26 (0.08) Worry subscale 1.1 (0.11)	Mean (SE) **DTSQs**: score 0-36, higher scores indicate higher treatment satisfaction **DTSQc:** score -18 to 18, higher positive scores indicate improved treatment satisfaction **HFS-II:** Behaviour scale 0–60, higher behaviour scores indicate greater tendency to avoid hypoglycaemia. Worry scale 0–72, higher scores indicate more worry	?	-	?

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.8
Outcome variable: Patient reported outcomes with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Non-randomised studies									
Bisio 2021 US	Non-randomised study (before/after)	18	3	**Hypoglycaemia fear survey** Total score 27.64 (14.107) Ns Behavioural subscale 14.57 (5.694) Ns Worry subscale 13.07 (9.434) Ns **Diabetes Distress Survey** Total score 1.35 (0.25) p=0.046 Emotional subscale 1.47 (0.42) Ns Regimen subscale 1.40 (0.33) Ns	**Hypoglycaemia fear survey** Total score 24.21 (12.448) Behavioural subscale 13.5 (5.431) Worry subscale 10.71 (8.588) **Diabetes Distress Survey** Total score 1.50 (0.36) Emotional subscale 1.64 (0.55) Regimen subscale 1.57 (0.48)	**HFS-II**: Total score 0-132, higher score indicates greater fear. Behaviour scale 0–60, higher behaviour scores indicate greater tendency to avoid hypoglycaemia. Worry scale 0–72, higher scores indicate more worry **DDS:** score 1-6, higher scores indicate more distress	+	-	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.8
Outcome variable: Patient reported outcomes with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
				Physician subscale 1.27 (0.32) Ns Interpersonal subscale 1.20 (0.33) p=0.028 **Center for Epidemiological Studies Depression Scale-Revised** 6.43 (6.88) Ns **Pittsburgh Sleep Quality Index** 5.5 (3.107) Ns	Physician subscale 1.27 (0.21) Interpersonal subscale 1.42 (0.48) **Center for Epidemiological Studies Depression Scale-Revised** 6 (7.952) **Pittsburgh Sleep Quality Index** 5.71 (4.232)	**CESD-R:** scale 0-60, higher scores indicate more depressive symptoms **PSQI:** scale 0-21, lower scores indicate better sleep			
Boscari 2022 Italy	Retrospective non-randomised study (before/after)	31	None	**Diabetes treatment satisfaction questionnaire** 33.0 (3.5) Mean of the differences (95% CI) 1.3 (0.4 to 2.2) p= 0.006 **Hypoglycaemia fear survey** Total score 26.3 (16.1) Mean of the differences (95% CI) -10.2 (-17.8 to -2.6)	**Diabetes treatment satisfaction questionnaire** 31.9 (3.0) **Hypoglycaemia fear survey** Total score 37.4 (22.0)	**DTSQ:** score 0-36, higher scores are positive **HFS-II**: Total score 0-132, higher score indicates greater fear. Behaviour scale	+	-	?

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.8
Outcome variable: Patient reported outcomes with validated instruments

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Mean (SD) unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
				p= 0.01 <u>Behaviour subscale</u> 13.0 (8.0) Mean of the differences (95% CI) -4.1 (-7.7 to -0.6) p= 0.02 <u>Worries subscale</u> 13.2 (9.3) Mean of the differences (95% CI) -6.1 (-10.6 to -1.6) p= 0.01 **Pittsburgh Sleep Quality Index** 4.3 (2.7) Mean of the differences (95% CI) -0.3 (-1.1 to 0.4) p= 0.35	<u>Behaviour subscale</u> 17.5 (9.3) <u>Worries subscale</u> 19.8 (14.3) **Pittsburgh Sleep Quality Index** 4.6 (2.2)	0–60, higher behaviour scores indicate greater tendency to avoid hypoglycaemia. <u>Worry scale</u> 0–72, higher scores indicate more worry **PSQI:** scale 0-21, lower scores indicate better sleep			

AHCL: advanced hybrid closed loop, CESD-R: Center for Epidemiological Studies Depression Scale- Revised, CI: confidence interval, DDS: Diabetes Distress Survey, DTSQ: Diabetes Treatment Satisfaction Questionnaire, DTSQc: Diabetes Treatment Satisfaction Questionnaire change, DTSQs: Diabetes Treatment Satisfaction Questionnaire status, HFS-II: Hypoglycaemia Fear Survey, iDCL trial: the International Diabetes Closed Loop trial, Ns: non-significant, PLGS: predictive low-glucose suspend, PSQI: Pittsburgh Sleep Quality Index, RCT: randomised controlled trial, SAP: sensor augmented pump, SD: standard deviation, SE: standard error, UK: The United Kingdom, US: The United States of America, VAS: Visual Analogical Scales

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.9
Outcome variable: Adverse events (other than severe hypoglycaemia and diabetic ketoacidosis)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Number of events unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop with multiple daily injections with insulin and sensor									
Choudhary 2022 France Germany UK	RCT with parallel design	82	7 I=5 C=2	Serious adverse events: 1 Number of diabetes-related hospitalizations: 0 Number of emergency room admissions: 0 Device deficiencies: 56 Non-serious adverse event: 66 (related to study device: 5 lipohypertrophy, 3 cannula site reaction, 2 sensor site reaction, 1 severe hyperglycaemia, 1 topical adhesive reaction, 1 bleeding at sensor site insertion, 1 skin reaction to infusion set, 1 infusion site rash) SUM: 123 p<0.0001	Serious adverse events: 1 Number of diabetes-related hospitalizations: 1 Number of emergency room admissions: 1 Device deficiencies: 8 Non-serious adverse event: 39 (related to study device: one itching at injection site, one bleeding at sensor insertion site, one device site erythema) SUM: 50	High-risk population	+	-	?

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.9
Outcome variable: Adverse events (other than severe hypoglycaemia and diabetic ketoacidosis)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Number of events unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Advanced hybrid closed loop with SAP with/without PLGS									
RCT									
Anderson 2019a US	RCT with parallel design	47	5 I=3 C=2	Serious adverse events: 0 Moderate hyperglycaemia with moderate ketonemia: 3 Mild ketonemia: 2 IV site bruising: 2 Soccer injury: 1 Upper respiratory illness: 1 Gastroenteritis with dehydration: 1 Fever and flu-like symptoms: 1 Ear infection: 1 Upper respiratory tract infection: 1 Vasovagal event during IV insertion: 1 SUM: 14 events p=0.5317 8 of 21 participants experienced 14 adverse events	Serious adverse events: 0 Mild/moderate hyperglycemia with mild/moderate ketonemia event: 4 IV site bruising: 1 Surgery for spiral fracture of right arm: 1 Mild fever: 1 Vasovagal event during CGM sensor insertion: 1 Vasovagal event after IV insertion: 1 Gastroenteritis: 1 SUM: 10 events 6 of 21 participants experienced 10 adverse events	High-risk population	?	-	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.9
Outcome variable: Adverse events (other than severe hypoglycaemia and diabetic ketoacidosis)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Number of events unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Benhamou 2019 France	RCT with cross-over design	68	5	Severe hyperglycaemia: 9 (in 4 patients) p=0.0144 4 of 63 participants experienced 9 adverse events	Severe hyperglycaemia: 0		+	?	-
Kovatchev 2020b Italy US	RCT with cross-over design	93	13	Device issues: Software error in Tandem Control-IQ for 8 participants Software error of mobile inControl in 12 participants		Unclear which group: 3 hyperglycaemias with ketosis 30 other adverse events (surgery, disease/infection/ condition)	+	?	-
Non-randomised studies									
Anderson 2016 US	Non-randomised study (before/after)	30	None	Severe adverse events other than hypoglycaemia and ketoacidosis: 0	Severe adverse events other than hypoglycaemia and ketoacidosis: 0		+	-	-
Bisio 2021 US	Non-randomised study (before/after)	18	3	Adverse events: 0	Adverse events: 0		+	-	-

Project: A comparison of advanced hybrid closed loop systems with multiple daily injections or SAP with/without PLGS in adults with diabetes type 1
Appendix 4.9
Outcome variable: Adverse events (other than severe hypoglycaemia and diabetic ketoacidosis)

* + No or minor problems
? Some problems
- Major problems

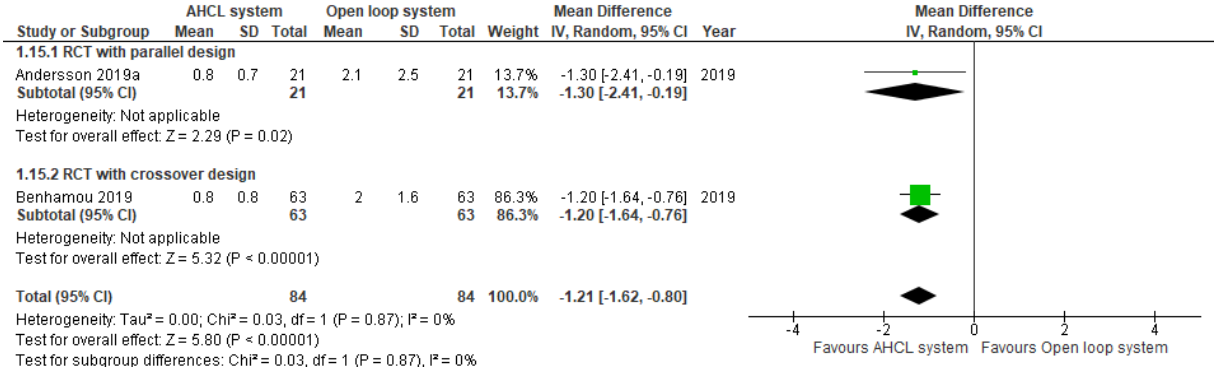
Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results Number of events unless otherwise stated		Comments	Directness *	Study limitations *	Precision *
				Intervention: AHCL	Control: multiple daily injections or SAP with/without PLGS				
Kovatchev 2017 Italy US	Non-randomised study (before/after) Extension (phase 2) of Anderson 2016 Compares to baseline data from phase 1 (Andersson 2016)	14	1	One participant had 2 episodes of ketones >1.0 mmol/l due to insulin pump occlusion		Compared to baseline data from phase 1; 2 weeks SAP (Andersson 2016)	?	-	-

AHLC: advanced hybrid closed loop, CGM: continuous glucose monitoring, HbA1c: haemoglobin A1c, IV: intravenous, PLGS: predictive low glucose suspend, RCT: randomised controlled trial, SAP: sensor augmented pump, UK: The United Kingdom, US: The United States of America

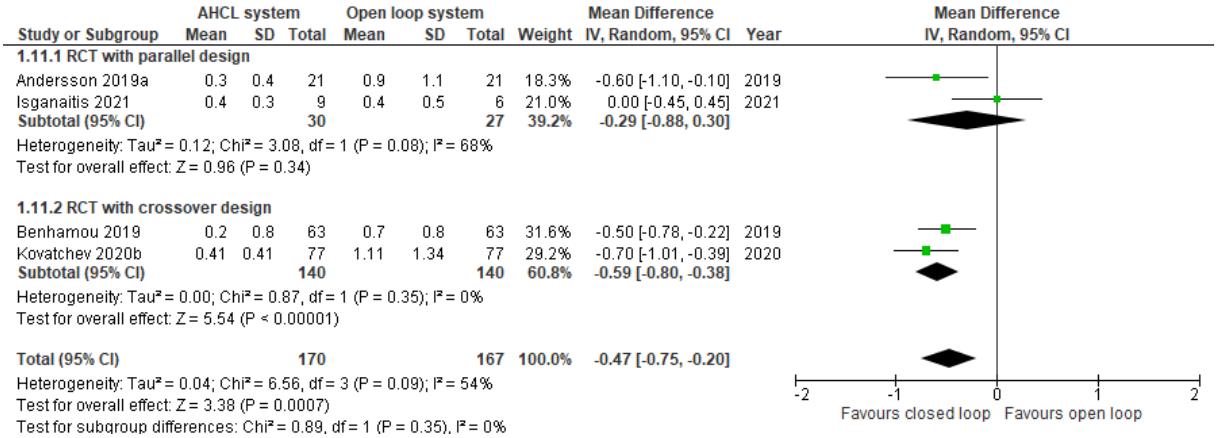
Appendix 5. Meta-analyses

RCTs

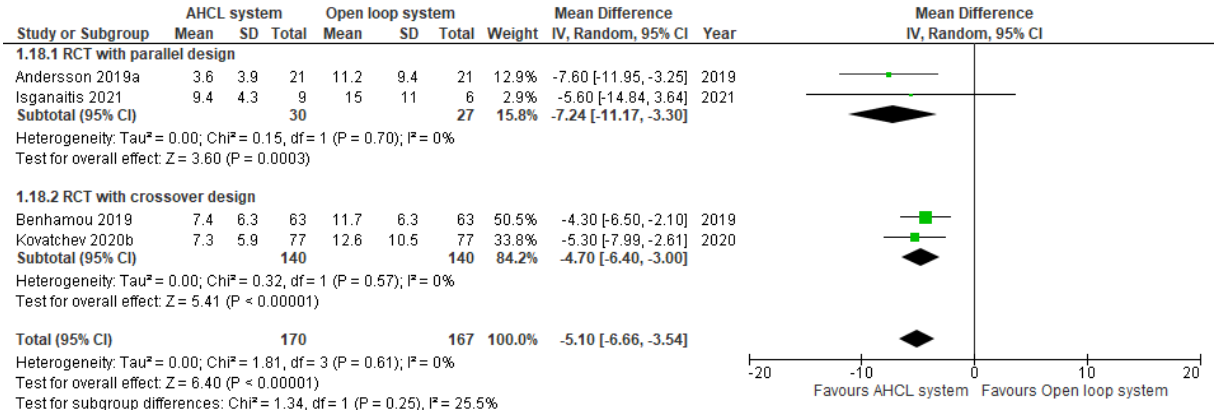
Time below 3.5 or 3.3 mmol/L, %



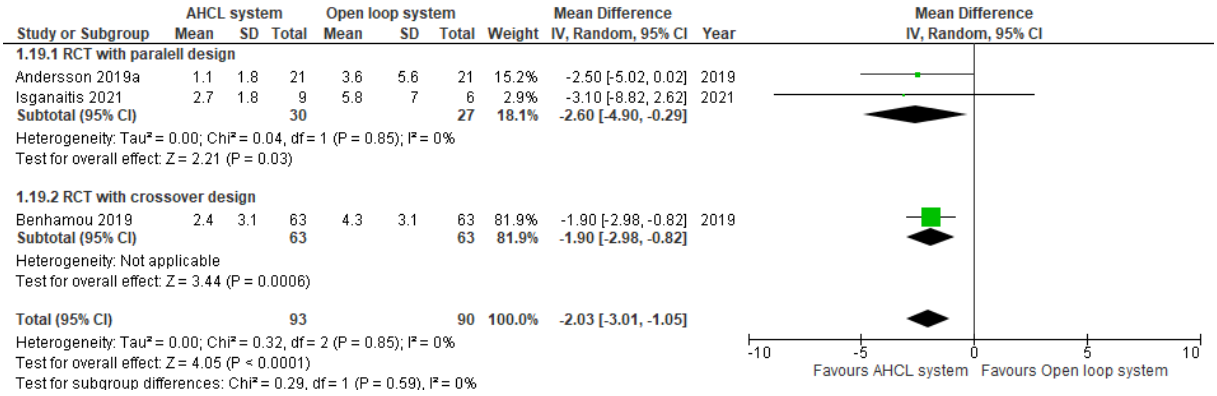
Time below 3.0 and <2.8 mmol/L, %



Time above 13.3 or 13.9 mmol/L, %

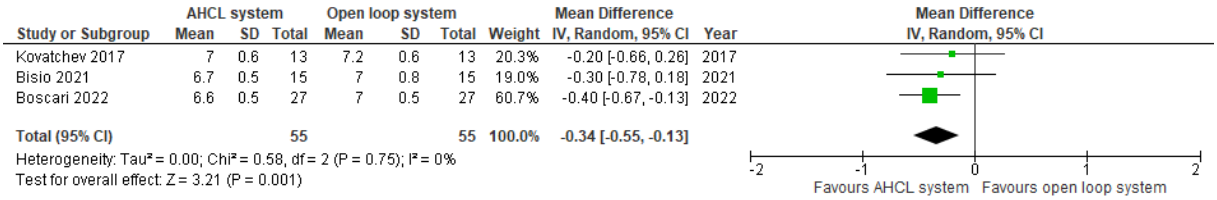


Time above 16.7 mmol/L, %

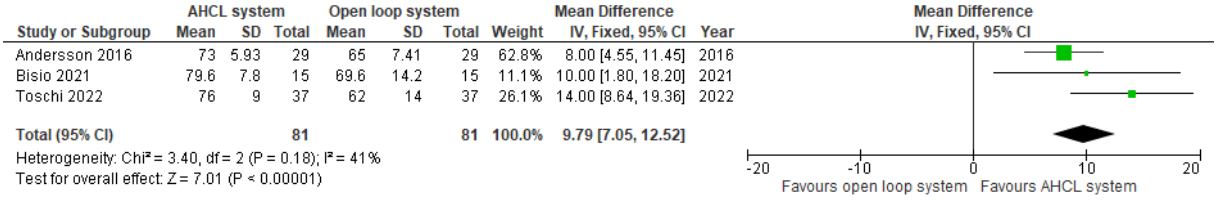


Non-randomised studies

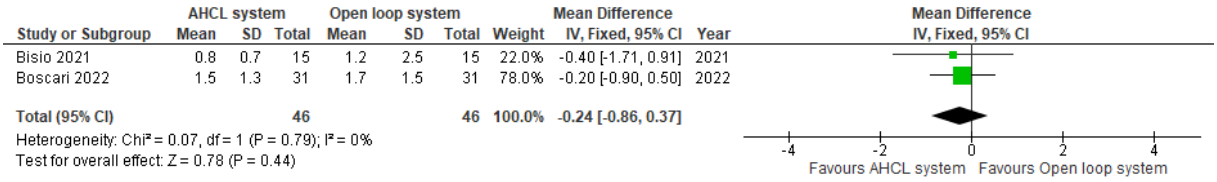
HbA1c, %



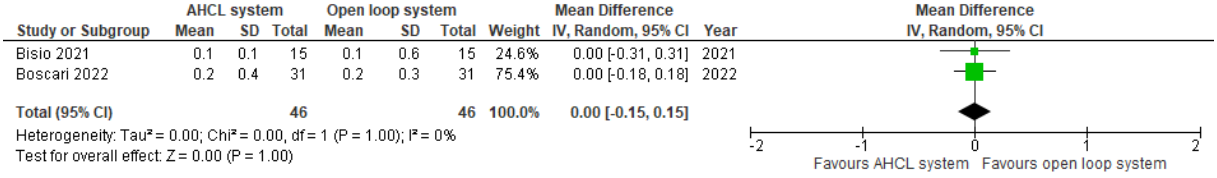
Time in range 3.9-10.0 mmol/L, %



Time below 3.9 mmol/L, %



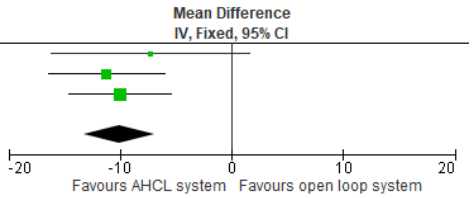
Time below 3.0 mmol/L, %



Time above 10.0 mmol/L, %

Study or Subgroup	AHCL system Mean	SD	Total	Open loop system Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Bisio 2021	19.3	8.1	15	26.6	15.5	15	13.1%	-7.30 [-16.15, 1.55]	2021
Boscari 2022	24.4	8	31	35.6	12.4	31	38.0%	-11.20 [-16.39, -6.01]	2022
Toschi 2022	20	9	37	30	11	37	48.9%	-10.00 [-14.58, -5.42]	2022
Total (95% CI)			**83**			**83**	**100.0%**	**-10.10 [-13.31, -6.90]**	

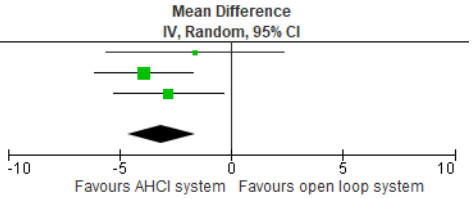
Heterogeneity: Chi² = 0.56, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 6.18 (P < 0.00001)



Time above 13.9 mmol/L, %

Study or Subgroup	AHCL system Mean	SD	Total	Open loop system Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Bisio 2021	2.56	3.6	15	4.18	7	15	14.5%	-1.62 [-5.60, 2.36]	2021
Boscari 2022	4.6	2.6	31	8.5	5.7	31	47.3%	-3.90 [-6.11, -1.69]	2022
Toschi 2022	3.2	3	37	6	7	37	38.2%	-2.80 [-5.25, -0.35]	2022
Total (95% CI)			**83**			**83**	**100.0%**	**-3.15 [-4.67, -1.63]**	

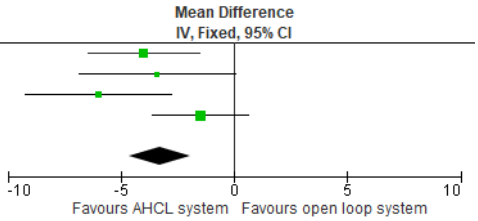
Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 4.07 (P < 0.0001)



Glucose variability (coefficient of variation of sensor glucose values), %

Study or Subgroup	AHCL system Mean	SD	Total	Open loop system Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Andersson 2016	34	4.44	29	38	5.19	29	28.9%	-4.00 [-6.49, -1.51]	2016
Bisio 2021	30.3	4.8	15	33.7	4.9	15	14.8%	-3.40 [-6.87, 0.07]	2021
Toschi 2022	29	8	37	35	6	37	17.2%	-6.00 [-9.22, -2.78]	2022
Boscari 2022	31.8	4.2	31	33.3	4.4	31	39.0%	-1.50 [-3.64, 0.64]	2022
Total (95% CI)			**112**			**112**	**100.0%**	**-3.28 [-4.62, -1.94]**	

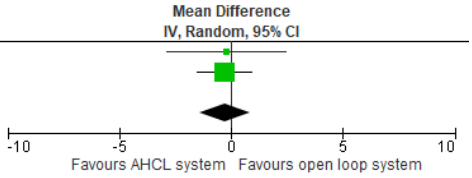
Heterogeneity: Chi² = 5.72, df = 3 (P = 0.13); I² = 48%
Test for overall effect: Z = 4.81 (P < 0.00001)



Pittsburgh Sleep Quality Index

Study or Subgroup	AHCL system Mean	SD	Total	Open loop system Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Bisio 2021	5.5	3.107	15	5.71	4.232	15	17.6%	-0.21 [-2.87, 2.45]	2021
Boscari 2022	4.3	2.7	31	4.6	2.2	31	82.4%	-0.30 [-1.53, 0.93]	2022
Total (95% CI)			**46**			**46**	**100.0%**	**-0.28 [-1.40, 0.83]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)



Hypoglycaemia fear survey

Study or Subgroup	AHCL system Mean	SD	Total	Open loop system Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.36.1 Total score									
Bisio 2021	27.64	14.107	15	24.21	12.448	15	50.1%	3.43 [-6.09, 12.95]	2021
Boscari 2022	26.3	16.1	31	37.4	22	31	49.9%	-11.10 [-20.70, -1.50]	2022
Subtotal (95% CI)			**46**			**46**	**100.0%**	**-3.82 [-18.06, 10.42]**	

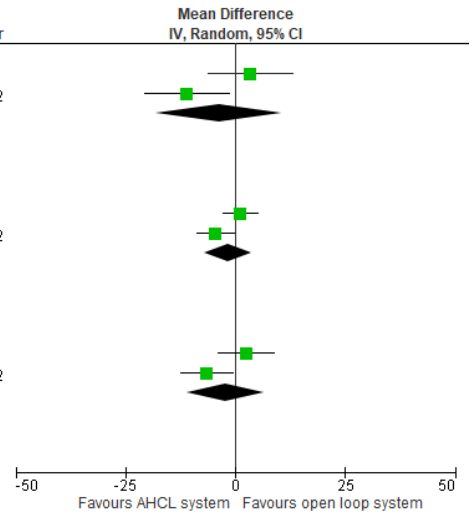
Heterogeneity: Tau² = 81.77; Chi² = 4.44, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.53 (P = 0.60)

1.36.2 Behavioural subscale									
Bisio 2021	14.57	5.694	15	13.5	5.431	15	51.2%	1.07 [-2.91, 5.05]	2021
Boscari 2022	13	8	31	17.5	9.3	31	48.8%	-4.50 [-8.82, -0.18]	2022
Subtotal (95% CI)			**46**			**46**	**100.0%**	**-1.65 [-7.11, 3.81]**	

Heterogeneity: Tau² = 11.02; Chi² = 3.45, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.59 (P = 0.55)

1.36.3 Worry subscale									
Bisio 2021	13.07	9.434	15	10.71	8.588	15	49.1%	2.36 [-4.10, 8.82]	2021
Boscari 2022	13.2	9.3	31	19.8	14.3	31	50.9%	-6.60 [-12.60, -0.60]	2022
Subtotal (95% CI)			**46**			**46**	**100.0%**	**-2.20 [-10.98, 6.58]**	

Heterogeneity: Tau² = 30.02; Chi² = 3.97, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 0.49 (P = 0.62)



Appendix 6. Costs per patient in eight scenarios

Treatment option 1. An example of estimated costs* of a patient with AHCL system MiniMed 780G (Region Västra Götaland)

Type of inputs	Inputs	Year 1	Year 2	Year 3	Year 4	Average Year 1-4	Share (%)
Device	MiniMed 780G	11,408	11,408	11,408	11,408	11,408	16.6%
Device maintenance	Infusion set Mio advance	14,640	13,537	11,573	9,149	12,225	61.9%
	Reservoir	4,080	3,773	3,225	2,550	3,407	
	Sender (1 per year)	-	4,161	3,557	2,812	2,633	
	Sensor Guardian Link 4 (change every 7 days)	24,205	24,762	21,170	16,736	21,718	
	Insulin total daily dose 50 units	3,084	2,852	2,438	1,927	2,575	
Staff	Doctor's contact	10,808	4,997	4,272	3,377	5,864	21.6%
	Nurse's contact	16,772	4,431	3,788	2,995	6,996	
	Dietitian visit	3,622	1,675	1,432	1,132	1,965	
Total		88,619	71,594	62,864	52,086	68,791	100.0%

*At price level of 2022 and 3% discounting rate applied

Treatment option 2. An example of estimated costs* of a patient with AHCL system Tandem t:slim X2 Control-IQ (Region Västra Götaland)

Type of inputs	Inputs	Year 1	Year 2	Year 3	Year 4	Average year 1-4	Share (%)
Device	Tandem t:slim X2 Control-IQ	10,819	10,819	10,819	10,819	10,819	14.0%
Device maintenance	Infusion set Autosoft 90	13,200	12,205	11,286	10,435	11,781	66.0%
	Reservoir	3,960	3,662	3,386	3,131	3,534	
	Sender (4 per year)	5,700	7,027	6,498	6,008	6,308	
	Sensor Dexcom G6 (change every 10 days)	28,186	28,362	26,224	24,248	26,755	
	Insulin total daily dose 50 units	3,084	2,852	2,438	1,927	2,575	
Staff	Doctor's contact	10,808	4,997	4,272	3,377	5,864	20.0%
	Nurse's contact	19,168	4,431	3,788	2,995	7,595	
	Dietitian visit	3,622	1,675	1,432	1,132	1,965	
Total		**98,547**	**76,029**	**70,143**	**64,072**	**77,198**	**100.0%**

*At price level of 2022 and 3% discounting rate applied

Treatment option 3. An example of estimated costs* of a patient with sensor augmented pump (SAP) MiniMed 740G (earlier 640G) (Region Västra Götaland)

Type of inputs	Inputs	Year 1	Year 2	Year 3	Year 4	Average year 1-4	Share
Device	MiniMed 740G (earlier 640)	9,443	9,443	9,443	9,443	9,443	14.6%
Device maintenance	Infusion set Mio advance	14,640	13,537	11,573	9,149	12,225	63.4%
	Reservoir	4,080	3,773	3,225	2,550	3,407	
	Sender Guardian Link 3 (1 per year)	4,500	4,161	3,557	2,812	3,758	
	Sensor Guardian Link 3 (change every 7 days)	21150	21,637	18,498	14,624	18,977	
	Insulin total daily dose 50 units	3,084	2,852	2,438	1,927	2,575	
Staff	Doctor's contact	10,808	4,997	4,272	3,377	5,864	22.0%
	Nurse's contact	14,376	4,431	3,788	2,995	6,397	
	Dietitian visit	3,622	1,675	1,432	1,132	1,965	
Total		**85,703**	**66,503**	**58,227**	**48,009**	**64,611**	**100.0%**

*At price level of 2022 and 3% discounting rate applied

Treatment option 4. An example of estimated costs* of a patient with SAP Tandem t:slim X2 Basal-IQ (Region Västra Götaland)

Type of inputs	Inputs	Year 1	Year 2	Year 3	Year 4	Average year 1-4	Share
Device	Tandem t:slim X2 Basal-IQ	9,609	9,609	9,609	9,609	9,609	13.2%
Device maintenance	Infusion set Autosoft 90	13,200	12,205	11,286	11,286	11,994	67.2%
	Reservoir	3,960	3,662	3,131	2,475	3,307	
	Sender (4 per year)	5,700	7,027	6,008	4,750	5,871	
	Sensor Dexcom G6 (change every 10 days)	28,186	28,362	24,248	19,169	24,991	
	Insulin total daily dose 50 units	3,084	2,852	2,438	1,927	2,575	
Staff	Doctor's contact	10,808	4,997	4,272	3,377	5,864	19.6%
	Nurse's contact	14,376	4,431	3,788	2,995	6,397	
	Dietitian visit	3,622	1,675	1,432	1,132	1,965	
Total		**92,545**	**74,818**	**66,211**	**56,719**	**72,573**	**100.0%**

*At price level of 2022 and 3% discounting rate applied

Treatment option 5. An example of estimated costs* of a patient with Omnipod DASH (patch pump) and a Dexcom sensor (Not SAP or AHCL) (Region Västra Götaland)

Type of inputs	Inputs	Year 1	Year 2	Year 3	Year 4	Total year 1-4	Share
Device	Handheld device	2,100	1,942	1,660	1,535	1,809	2.7%
Device maintenance	Podcasts	22,204	20,531	17,553	13,876	18,541	77.3%
	Sender (4 per year)	5,700	7,027	6,008	4,750	5,871	
	Sensor Dexcom G6 (change every 10 days)	30,673	28,362	24,248	19,169	25,613	
	Insulin total daily dose 50 units	3,084	2,852	2,438	1,927	2,575	
Staff	Doctor's contact	10,808	4,997	4,272	3,377	5,864	20.0%
	Nurse's contact	11,980	4,431	3,788	2,995	5,798	
	Dietitian visit	3,622	1,675	1,432	1,132	1,965	
Total		**90,171**	**71,815**	**61,399**	**48,761**	**68,037**	**100.0%**

*At price level of 2022 and 3% discounting rate applied

Treatment option 6. An example of estimated costs* of a patient with Omnipod DASH (patch pump) and a Libre 3 sensor (Not SAP or AHCL) (Region Västra Götaland)

Type of inputs	Inputs	Year 1	Year 2	Year 3	Year 4	Average year 1-4	Share
Device	Handhold device	2,100	1,942	1,660	1,312	1,754	3.7%
Device maintenance	Podcasts	22,204	20,531	17,553	13,876	18,541	67.4%
	Sensor FreeStyle Libre 3 (change every 14 days)	12,740	11,780	10,071	7,962	10,638	
	Insulin total daily dose 50 units	3,084	2,852	2,438	1,927	2,575	
Staff	Doctor's contact	10,808	4,997	4,272	3,377	5,864	28.9%
	Nurse's contact	11,980	4,431	3,788	2,995	5,798	
	Dietitian visit	3,622	1,675	1,432	1,132	1,965	
Total		**66,538**	**48,206**	**41,214**	**32,581**	**47,135**	**100.0%**

*At price level of 2022 and 3% discounting rate applied

Treatment option 7. An example of estimated costs* of a patient with multiple daily insulin injections and a Dexcom sensor (Region Västra Götaland)

Type of inputs	Inputs	Year 1	Year 2	Year 3	Year 4	Average year 1-4	Share
Device and maintenance	Sender (4 per year)	7,600	7,027	6,008	4,750	6,346	78.6%
	Sensor Dexcom G6 (change every 10 days)	30,673	28,362	24,248	19,169	25,613	
	Insulin total daily dose 50 units	5832	5,393	4,610	3,645	4,870	
Staff	Doctor's contact	5,404	4,997	4,272	3,377	4,513	21.4%
	Nurse's contact	4,792	4,431	3,788	2,995	4,001	
	Dietitian visit	1,811	1,675	1,432	1,132	1,512	
Total		**56,112**	**51,883**	**44,358**	**35,067**	**46,855**	**100%**

*At price level of 2022 and 3% discounting rate applied

Treatment option 8. An example of estimated costs* of a patient with multiple daily insulin injections and a FreeStyle Libre 3 sensor (Region Västra Götaland)

Type of inputs	Inputs	Year 1	Year 2	Year 3	Year 4	Average year 1-4	Share
Device and maintenance	Sensor FreeStyle Libre 3 (change every 14 days)	12,740	11,780	10,071	7,962	10,638	60.7%
	Insulin total daily dose 50 units	5,832	5,393	4,610	3,645	4,870	
Staff	Doctor's contact	5,404	4,997	4,272	3,377	4,513	39.3%
	Nurse's contact	4,792	4,431	3,788	2,995	4,001	
	Dietitian visits	1,811	1,675	1,432	1,132	1,512	
Total		**30,579**	**28,275**	**24,174**	**19,110**	**25,534**	**100%**

*At price level of 2022 and 3% discounting rate applied

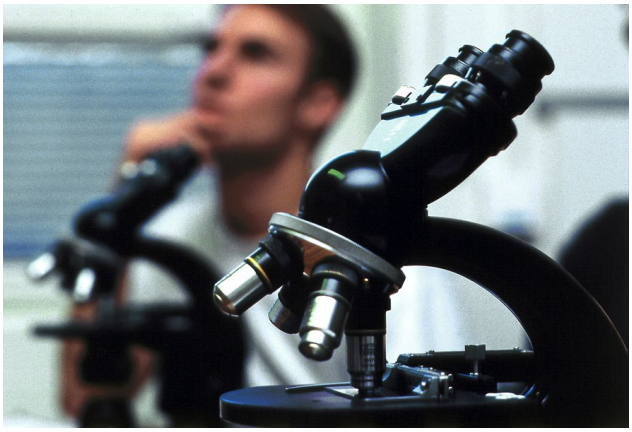
Innehållsdeklaration

Denna HTA-rapport är baserad på följande moment:

- [x] Metodbeskrivning
- [x] PICO
- [x] Uttömmande litteratursökning
- [x] Flödesschema
- [x] Urval relevans
- [x] Kvalitetsgranskning
- [x] Tabelldata
- [x] Sammanvägning av resultat
- [x] Metaanalys
- [x] Evidensgradering enligt GRADE
- [x] Sammanfattning
- [x] Ekonomi
- [x] Organisation
- [x] Etik
- [x] Pågående studier
- [x] Exkluderade artiklar
- [x] Expertgrupp deltar
- [x] Extern granskning
- [x] Kunskapsluckor identifierade
- [x] Jävsdeklaration inhämtad från projektdeltagarna

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

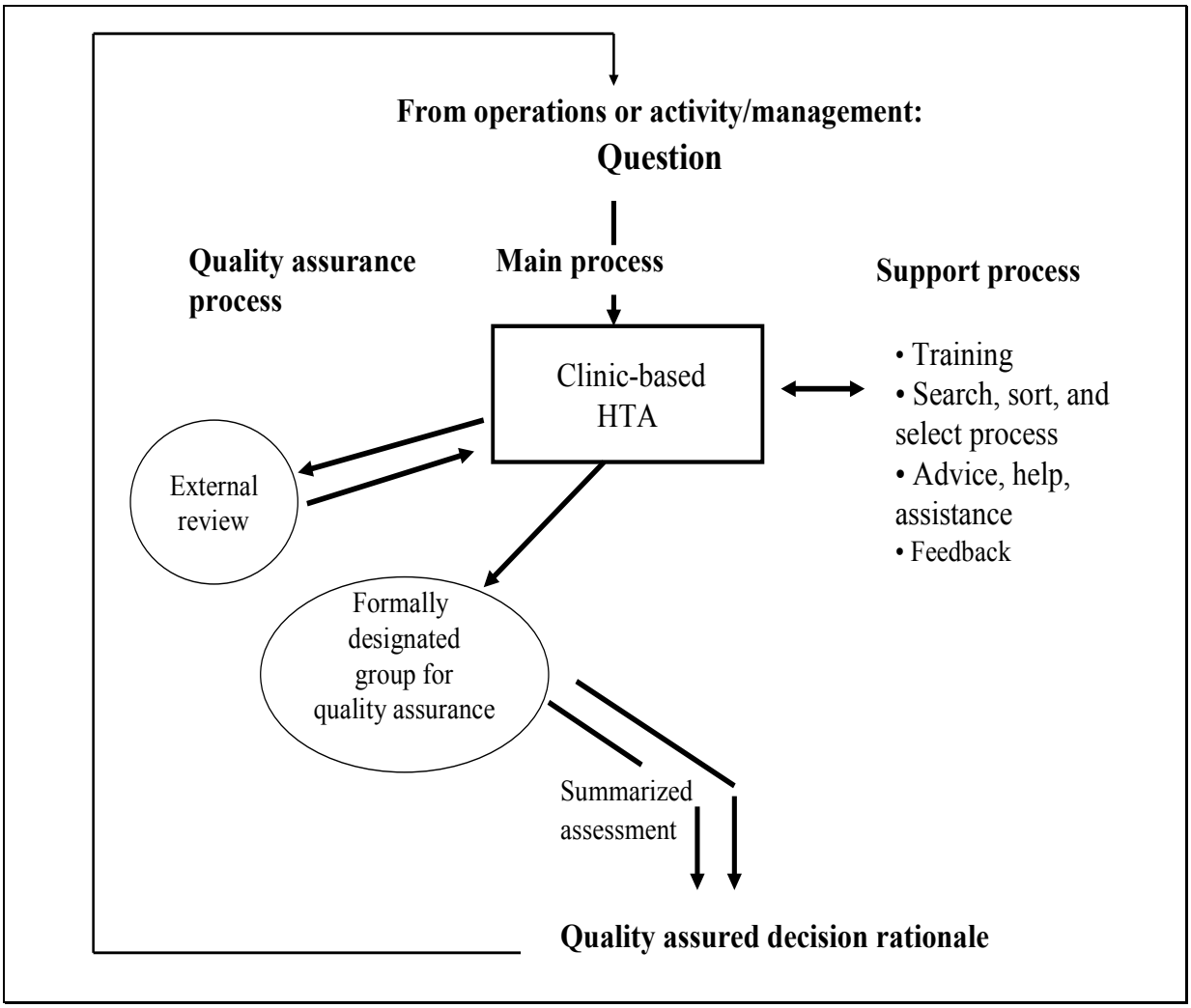
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
Professor, MD
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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