CORE-MD

Coordinating Research and Evidence for Medical Devices

High Risk CE-Marked Medical Devices for Diabetes Care

A Systematic Review and Meta-analysis

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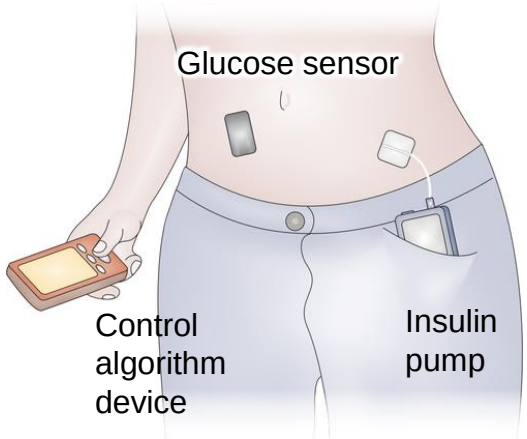
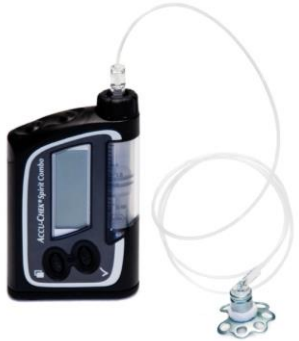
Classes of Devices

- Implantable continuous glucose monitoring systems (CGM)
- Implantable insulin pumps
- Automated insulin delivery systems (AID)
  -Hybrid closed loop systems
  -Fully closed loop systems





Accu-Chek DiaPort System

Medtronic Minimed 780G

t:slim X2 with Control-IQ Technology

Accu-Chek Insight with DBLG1 from Diabeloop

Mylife CamAPS Fx

List of Medical Devices

Class of device	Device	Manufacturer	CE-Mark approval date
Implantable CGM devices	Implantable Eversense ® CGM sensor	Senseonics Inc	2016
Implantable Insulin Pumps	MiniMed MIP2007C	Medtronic	2013
	DiaPort ®	Roche	2012
Automated insulin delivery devices			
Hybrid closed-loop systems	MiniMed 670G	Medtronic	2018
	Minimed 770G	Medtronic	2020
	MiniMed 780 G	Medtronic	2020
	Control-IQ	Tandem	2020
	Diabeloop	Diabeloop	2018
	Inreda Diabetic	Inreda	2016
	Tidepool Loop	Tidepool	Pending
	Omnipod 5 system	Insulet	2022
	iLet Bionic Pancreas System	Medtech Beta Bionics	Pending
	CamAPS FX*	CamDiab	2020
Fully closed-loop systems	CamAPS HX	CamDiab	2020

Rationale

- The clinical evidence that is submitted for regulatory approval is not transparent
- A systematic review and meta-analysis of the evidence on the efficacy and safety of high-risk devices approved for managing diabetes in Europe is lacking

Aim

- To conduct a systematic review and meta-analysis assessing whether CE-marked high risk medical devices for diabetes management are safe and effective
- Reviewing study designs, statistical methods, reported outcomes and overall quality of evidence

Open access Protocol

BMJ Open

Clinical evidence for high-risk medical devices used to manage diabetes: protocol for a systematic review and meta-analysis

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PROSPERO (CRD42022366871)

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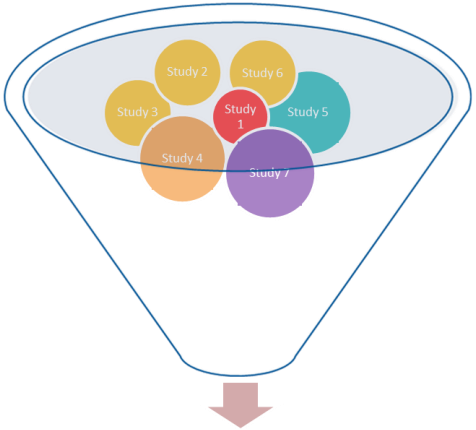
Search Strategy

Databases

- Medline All (Ovid)
- Embase (Elsevier)
- Cochrane Library (Wiley)
- Web of Science Core Collection
  - -Science Citations index
  - -Emerging Sources
- Eudamed database
- Swissmedic, notified bodies, manufacturers



Search Strategy

Inclusion Criteria

- Studies evaluating efficacy and/or safety of high risk CE-marked medical devices for diabetes care
- Observational and experimental design (pre- and post-market)
- In humans

Exclusion Criteria

- Letters to editor, proceedings, reviews, systematic reviews, meta-analysis, conference abstracts, expert opinion, animal studies

Search Strategy

- Participants: Patients with diabetes (both pediatric and adults)
- Intervention: High risk CE-marked medical devices for diabetes
- Comparator: Any (No intervention, active intervention, sham procedure)
- Outcomes:
  - Efficacy: Glucose control, acute and chronic glucose related complications
  - Safety: Severe hypoglycemia, diabetic ketoacidosis, device related SAE, device deficiencies, field safety notices

Search Strategy

- With help of a medical information specialist
- Embase 2475 hits
- 200 first abstracts screened to adapt search strategy
- Search strategy converted to the other databases

#13	#9 AND #12	2,475
#12	#10 OR #11	9,800,162
#11	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'retrospective study'/de OR 'cross-sectional study'/de OR 'observational study'/de OR 'population research'/de OR 'case control study'/exp OR 'case study'/exp OR 'major clinical study'/de OR cohort*:ab,ti OR (((prospectiv* OR populat* OR observ* OR retrospect* OR epidemiologic*) NEAR/3 (stud* OR trial*)):ab,ti) OR ((case* NEAR/3 control*):ab,ti) OR ((case* NEAR/3 series):ab,ti) OR ((cross NEAR/1 section*):ab,ti) OR 'case cohort*':ab,ti OR 'nested case control*':ab,ti OR prospectiv*:ab,ti OR longitudinal*:ab,ti OR 'follow up':ab,ti OR followup:ab,ti OR population-based:ab,ti	8,541,018
#10	random*:ti,ab OR placebo*:ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR 'triple blind*':ti,ab OR ((clinical NEXT/1 trial*):ti,ab) OR 'randomized controlled trial'/exp	2,371,004
#9	#7 NOT #8	15,370
#8	[animals]/lim NOT [humans]/lim	6,069,793
#7	#5 AND #6	15,915
#6	#3 OR #4	22,590
#5	#1 OR #2	1,326,262
#4	'ambulatory insulin infusion pump*':ti,ab OR 'artificial pancreas':ti,ab OR 'artificial endocrine pancreas':ti,ab OR 'automated pancreas':ti,ab OR 'automated insulin delivery':ti,ab OR 'automated insulin therapy':ti,ab OR 'automated insulin dosing':ti,ab OR 'bionic pancreas':ti,ab OR 'closed-loop control':ti,ab OR 'closed-loop system':ti,ab OR 'continuous intraperitoneal insulin infusion*':ti,ab OR 'do-it-yourself automated pancreas':ti,ab OR 'hybrid closed-loop':ti,ab OR 'implantable glucose monitor*':ti,ab OR 'implantable continuous glucose monitor*':ti,ab OR 'implanted insulin pump*':ti,ab OR 'implantable insulin pump*':ti,ab OR 'implanted infusion pump*':ti,ab OR 'implantable infusion pump*':ti,ab OR 'implantable cgm*':ti,ab OR 'sensor-augmented pump*':ti,ab OR 'implantable glucose sensor*':ti,ab OR 'medtronic 670g':ti,ab,dn,df OR minimed*:ti,ab,dn,df OR diaport*:ti,ab,dn,df OR 'control iq*':ti,ab,dn,df OR diabeloop*:ti,ab,dn,df OR tidepool*:ti,ab,dn,df OR 'omnipod* 5':ti,ab,dn,df OR 'ilet bionic pancreas*':ti,ab,dn,df OR eversense*:ti,ab,dn,df OR 'camaps hx*':ti,ab,dn,df OR 'camaps fx*':ti,ab,dn,df OR dblg1*:ti,ab,dn,df OR (((closed OR hybrid) NEAR/3 insulin NEAR/3 (system* OR delivery OR device* OR therapy OR algorithm)):ti,ab)	9,839
#3	'artificial pancreas'/exp OR 'closed loop control'/de OR 'closed loop control system'/de OR 'closed loop insulin delivery'/de OR 'closed loop insulin delivery system'/de OR 'continuous glucose monitoring device'/de OR 'glucose monitoring/insulin pump system'/de OR 'hybrid closed loop system'/de OR 'implantable drug delivery system'/de OR 'implantable infusion pump'/de OR 'insulin delivery device'/de OR 'insulin implant'/exp OR 'insulin pump therapy'/de	3,306
#2	diabet*:ti,ab OR hypoglycemi*:ti,ab OR hypoglycaemi*:ti,ab OR hyperglycemi*:ti,ab OR hyperglycaemi*:ti,ab OR 'iddm':ti,ab OR 'niddm':ti,ab OR 't1dm':ti,ab OR 't2dm':ti,ab	1,132,109
#1	'diabetes mellitus'/de OR 'insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'/de	965,852

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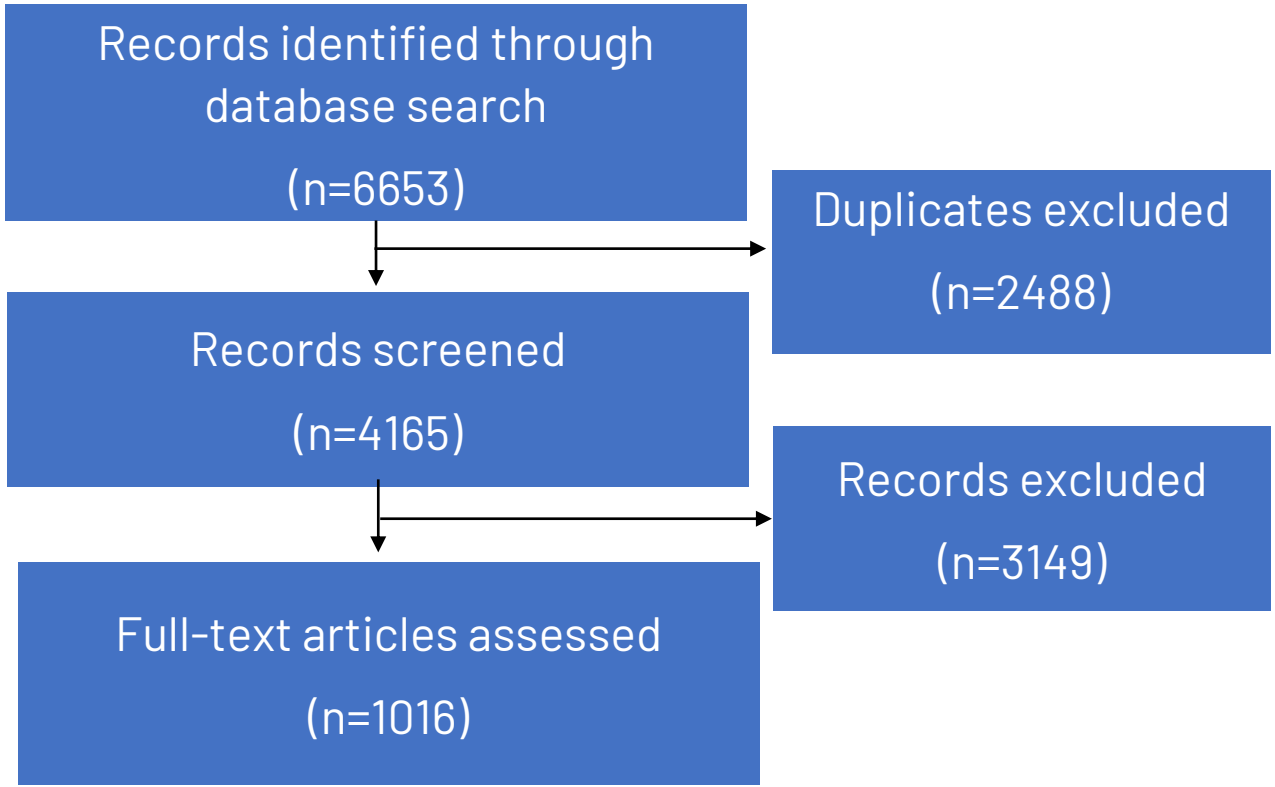
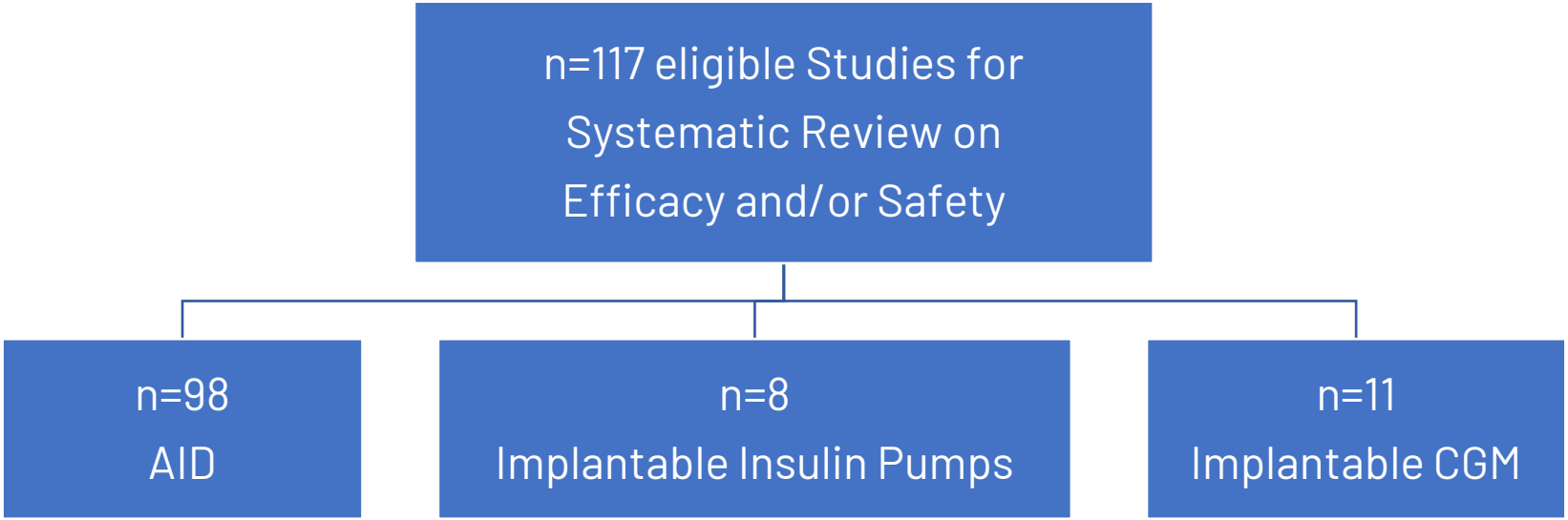
Methodology

- Narrative synthesis of the findings
- Meta-analysis of RCTs that compared AID systems with other therapies for diabetes management
- Meta-analysis of studies that compared outcomes before and after utilization of AID systems
- Assessment of heterogeneity
- Assessment of quality

Study Selection

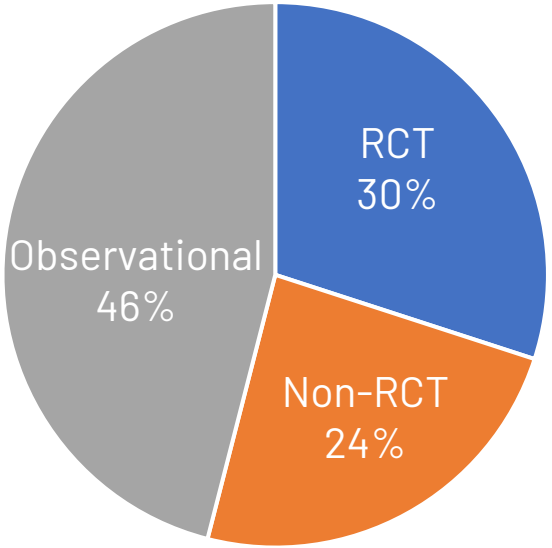



n=117 eligible Studies for Systematic Review on Efficacy and/or Safety
n=98 AID
n=8 Implantable Insulin Pumps
n=11 Implantable CGM

Results

- Studies published 2009-2022
- 41% industry funding
- 18% pre- market; 82% post- market

Study designs



Results

- Median sample size: 52 participants (IQR: 25-115)
- Predominantly type 1 diabetes
- Predominantly aged ≥18 years

- Median max follow-up: 13 weeks (IQR: 4-26)

- 47% of studies had a comparator group

Outcome reporting

- Efficacy outcomes

- 61 studies on HbA1c
- 101 studies on Time in range (%)
- No studies reported on chronic glucose related complications

Outcome reporting

Meta-analyses of RCTs comparing AID systems with other antidiabetic treatments

Outcome	N studies	Pooled mean difference (95% CI)
HbA1c (%)	N=9	**-0.22 (-0.28; -0.17)**
Time in range (%) (glucose 3.9-10 mmol/l)	N=16	**8.79 (8.03; 9.55)**

Outcome reporting

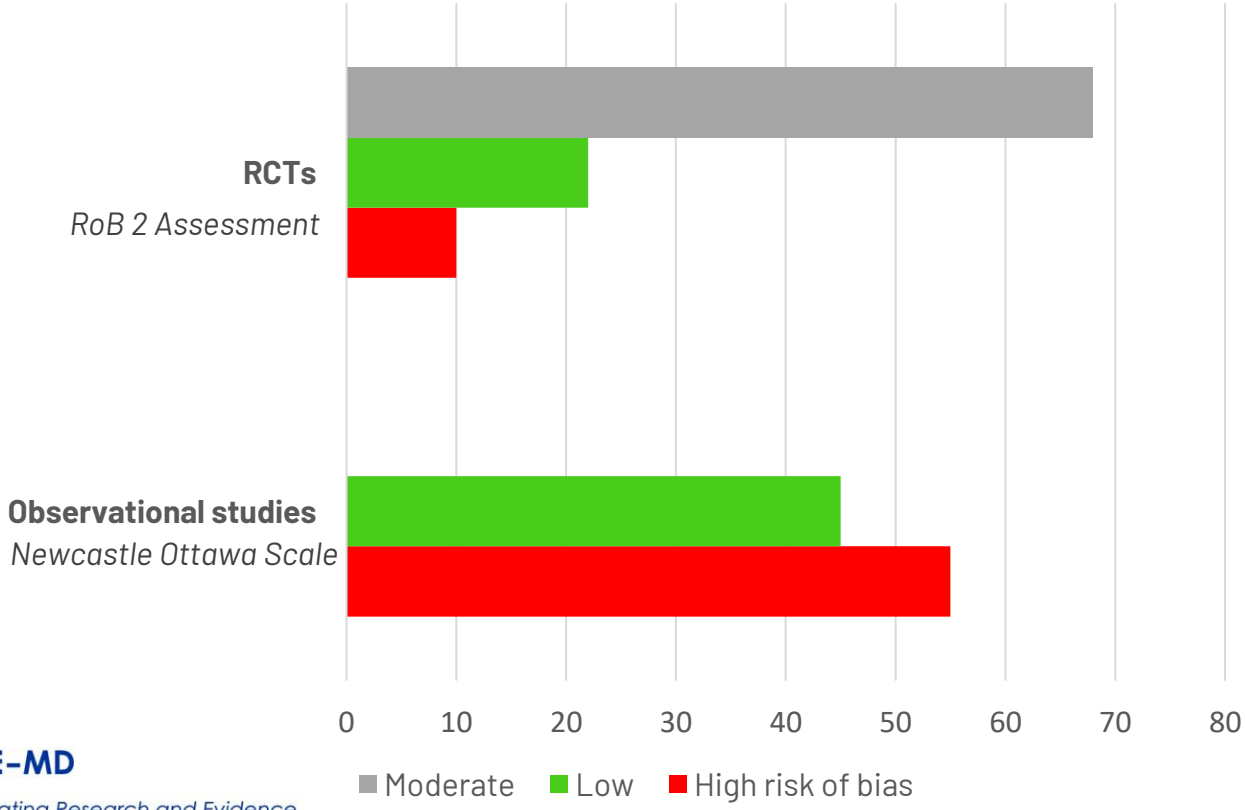
Meta-analyses of studies comparing outcomes before and after utilization of AID systems

Outcome	N studies	Pooled mean difference (95% CI)
HbA1c (%)	N=24	**-0.63 (-0.65; -0.61)**
Time in range (%) (glucose 3.9-10 mmol/l)	N=37	**10.64 (10.55; 10.73)**

Outcome reporting

- Safety outcomes
  - 71 studies reported on at least one safety outcome
  - Incomplete reporting
  - Frequency of safety outcomes was generally similar between intervention and control groups

Risk of Bias Assessment



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Conclusions

- CE-marked medical devices, in particular AID systems, improve glucose control
- However, no studies reported on chronic glucose related complications, and safety outcomes were partially reported across studies.

Conclusions

- Evidence is characterized by small studies with short follow-up time and methodological heterogeneity
- Need for developing standards for future investigations, thereby improving study comparability and transparency of findings

CORE-MD, Coordinating Research and Evidence for Medical Devices, aims to translate expert scientific and clinical evidence on study designs for evaluating high-risk medical devices into advice for EU regulators.

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For more information, visit: www.core-md.eu

ESC
EFORT – JOINT EFFORTS
Biomedical Alliance in Europe
European Academy of Paediatrics
Paediatric Section of U.E.M.S
EPF European Patients Forum
LUMC Leiden University Medical Center
University of Oxford
Region Uppsala
RCSI University of Medicine and Health Sciences
INSELSPITAL
Universitätsspital Bern
Hôpital universitaire de Berne
KU LEUVEN
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