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Clinical evidence for high-risk CE-marked medical devices for glucose management: A systematic review and meta-analysis

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Abstract

Aims: To conduct a systematic review and meta-analysis, within the Coordinating Research and Evidence for Medical Devices (CORE-MD) project, evaluating CE-marked high-risk devices for glucose management.

Materials and Methods: We identified interventional and observational studies evaluating the efficacy and safety of eight automated insulin delivery (AID) systems, two implantable insulin pumps, and three implantable continuous glucose monitoring (CGM) devices. We meta-analysed randomized controlled trials (RCTs) comparing AID systems with other treatments.

Results: A total of 182 studies published between 2009 and 2024 were included, comprising 166 studies on AID systems, six on insulin pumps, and 10 on CGM devices; 26% reported industry funding; 18% were pre-market; 37% had a comparator group. Of the studies identified, 29% were RCTs, 24% were non-randomized trials, and 47% were observational studies. The median (interquartile range) sample size was 48 (28–102), age 34.8 (14–44.2) years, and study duration 17.5 (12–26) weeks. AID systems lowered glycated haemoglobin by 0.5

Markus Laimer and Lia Bally are authors who indicate a shared contribution.

percentage points (absolute mean difference [MD] = −0.5; 21 RCTs; I^2 = 86%) and increased time in target range for sensor glucose level by 13.4 percentage points (MD = 13.4; 14 RCTs; I^2 = 90%). At least one safety outcome was assessed in 71% of studies.

Conclusions: High-risk devices for glucose monitoring or insulin dosing, in particular AID systems, improve glucose control safely, but evidence on diabetes-related end-organ damage is lacking due to short study durations. Methodological heterogeneity highlights the need for developing standards for future pre- and post-market investigations of diabetes-specific high-risk medical devices.

KEYWORDS
glycaemic control, meta-analysis, systematic review, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

During recent decades, methods for glucose monitoring and insulin dosing in diabetes care have changed profoundly and the ability to control glucose levels has improved significantly.[1] The development of several medical devices such as insulin pumps, continuous glucose monitoring (CGM) and automated insulin delivery (AID) systems, has greatly contributed to this progress.[2–4] Some of the devices belong to the high-risk category as they involve either automated drug delivery or implanted components.

Medical devices are classified according to their potential risks. According to the European Medical Device Regulation (MDR; EU 2017/745), high-risk devices include software that support or sustain human life or prevent impairment of human health but, when used, pose high risks to patients.[5] To obtain access to the European market, manufacturers need to submit their clinical data to a notified body authorized to issue a CE (*Conformité Européenne*) certificate. The CE mark indicates only that the device has a positive benefit/risk balance and that it complies with current standards. However, standards and guidance (such as ISO 14155 and European Union [EU] MDR 2017/745) do not precisely specify the clinical evidence that is needed for EU certification. Synthesizing the publicly available evidence for clinical investigations of diabetes-specific high-risk medical devices and exchanging information about their efficacy and safety profiles may be the first step to increase transparency and to identify what regulatory guidance is needed.[6]

The Coordinating Research and Evidence for Medical Devices (CORE-MD) project comprises a unique European collaboration that was developed to review methodologies for the clinical investigation and evaluation of high-risk medical devices. In the CORE-MD framework, we first identified CE-marked glucose management devices, which fall into the high-risk category, according to MDR. We then searched for evidence generated by these devices, either before or after CE certification, and conducted a systematic review and meta-analysis of the efficacy and safety of high-risk medical devices for diabetes management that are licensed for use in Europe.[7]

2 | METHODS

2.1 | Identification of high-risk CE-marked medical devices for diabetes care

The MDR specifies criteria to define high-risk medical devices (Classes IIb and III).[5] For the purpose of glucose management (e.g., glucose monitoring and insulin dosing), these include implantable CGM systems, implantable pumps (regardless of mode of insulin delivery), and AID systems (software as a medical device). Given the current lack of a complete and fully functional database listing CE-marked devices, we procured the necessary information as follows: (1) press releases available online, or scientific publications, mentioning the date of CE marking and (2) information provided by device manufacturers upon request. Additional details on the identification of high-risk medical devices for diabetes care is provided in the protocol of our manuscript.[8] Table 1 lists the eligible medical devices.

2.2 | Search strategy and study selection

We conducted our systematic review in accordance with the methodological principles outlined in the Cochrane Handbook and followed the reporting guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement 2020.[9,10] The protocol for the systematic review was published (PROSPERO: CRD42022366871).[8] A medical information specialist searched four electronic databases, including Embase (Elsevier), Medline All (Ovid), Cochrane Library (Wiley), Science Citation Index Expanded and Emerging Sources Citation Index (Web of Science), from inception to 27 March 2024 (Appendix S1).

We selected studies that: (1) had an observational or experimental design, including randomized controlled trials (RCTs), non-randomized trials, cohort studies, case–control studies, cross-sectional studies, and case series; (2) were performed in people with hyperglycaemia or diabetes; and (3) evaluated the efficacy and/or safety of

TABLE 1 List of high-risk CE-marked medical devices for glucose management.

Class of device	Device				Manufacturer	CE-mark approval date	Age limitation (years)
Implantable CGM devices	Eversense® CGM system (90 days) Eversense® XL CGM system (180 days) Eversense® E3 CGM sensor (6 months)				Senseonics Inc	2016 2017 2022	≥18 ≥18 ≥18
Implantable insulin pumps	MiniMed MIP2007C				Medtronic	2013	≥18
	AccuChekDiaPort®				Roche	2012	≥18
AID systems	*AID system*	*Compatible insulin pump*	*Compatible CGM system*	*Algorithm hosting*			
Hybrid closed-loop systems	MiniMed 670G system	MiniMed 670G pump	Guardian 3	Pump	Medtronic	2018	≥7
	MiniMed 780G system	MiniMed 780G pump	Guardian 3 Guardian 4 Simplera Sync	Pump	Medtronic	2020	≥7
	Control-IQ	Tandem t: slim X2	Dexcom G6, G7 and Freestyle Libre 3	Pump	Tandem Diabetes Care	2020	≥6
	DBLG1	Kaleido patch pump, Accu-Chek Insight pump	Dexcom G6	App on a hand-held device	Diabeloop	2018	≥18
	Omnipod 5 system	Omnipod 5 ACE pump	Dexcom G6 and Freestyle Libre 3	Pod[b]	Insulet	2022	≥2
	CamAPS FX	Dana RS, Dana-i, mylife YpsoPump	Dexcom G6, Freestyle Libre 3	App on smartphone	CamDiab	2020	≥1
Fully closed-loop systems	CamAPS HX	Dana RS, Dana-i, mylife YpsoPump	Dexcom G6, Freestyle Libre 3	App on smartphone	CamDiab	2020[c]	≥18
	Inreda AP[a]	Inreda dual chamber pump	Two Guardian sensors Two Medtronic Enlite sensors	Pump	Inreda Diabetic	2020	≥18

Abbreviations: ACE, alternate-controller enabled pump; AID, automated insulin delivery; CGM, continuous glucose monitoring.
[a]Bihormonal pump.
[b]Controlled from Omnipod 5 controller or phone App.
[c]CE-mark approval but not commercially available.

high-risk CE-marked medical devices used for the management of diabetes, both pre- and post-market, in comparison with any control group (active intervention, sham procedure, placebo or no intervention).

Outcomes related to efficacy included: metrics of glucose control, such as glycated haemoglobin (HbA1c; reflecting average blood glucose concentrations for the past 2–3 months); metrics calculated from plasma glucose or interstitial glucose concentrations (e.g., proportion of values within, above and below the glucose target range), according to an international consensus statement[11]; and diabetes-specific end-organ damage. Outcomes related to safety and device quality included severe hypoglycaemia, diabetic ketoacidosis, other device-related serious adverse events (SAEs), device deficiencies with SAE potential and device deficiencies (e.g., malfunction, misuse and inadequate labelling).[12] Appendix S2 provides details of search strategy, study selection, and data extraction.

2.3 | Quality assessment

Two reviewers independently rated the quality of studies (Appendix S3). In case of disagreement, a third reviewer was consulted. We assessed the quality of evidence using the Cochrane Risk of Bias Assessment Tool for RCTs,[13] the Newcastle–Ottawa Scale for observational studies,[14] and the National Institute of Health assessment tool for before–after (pre–post) studies without control groups.[15]

2.4 | Statistical analyses

We meta-analysed RCTs that compared AID systems with other therapies for diabetes treatment. Effect estimates were pooled using random-effects models as described by DerSimonian and

TABLE 2 Summary of study characteristics for the different classes of high-risk CE-marked medical devices in the field of diabetes.

Study characteristics	Overall	Implantable CGM devices	Implantable insulin pumps	AID systems
Number of studies	**182**	**10**	**6**	**166**
Geographic area, *n* (%)				
Europe	76 (41.8)	4	6	66
North America	65 (35.7)	5	–	60
South America	3 (1.7)	–	–	3
Asia	7 (3.8)	–	–	7
Africa	3 (1.7)	–	–	3
Australia/Oceania	13 (7.1)	–	–	13
Multiple	8 (4.4)	1	–	7
Not reported	7 (3.9)	–	–	7
Publication year, *n* (%)				
2009–2010	3 (1.7)	–	3	–
2011–2015	4 (2.2)	–	3	1
2016–2020	35 (19.2)	7	–	28
2021–2024	140 (76.9)	3	–	137
Funding source, *n* (%)				
Industry-funded	48 (26.4)	6	2	40
Non industry-funded	44 (24.2)	–	–	44
Both	31 (17.0)	2	–	29
None	33 (18.1)	1	–	32
Not declared	26 (14.3)	1	4	21
CE mark approval,[a] *n* (%)				
Pre-market study	33 (18.1)	2	4	27
Post-market study	121 (66.5)	8	2	111
Not reported	28 (15.3)	–	–	28
Study design, *n* (%)				
RCTs	53 (29.1)	2	3	48
Observational studies	86 (47.3)	3	3	80
Non-RIS	43 (23.6)	5	-	38
Study setting, *n* (%)				
Unsupervised outpatient setting	168 (92.3)	10	6	152
Other[b]	14 (7.7)	–	–	14
Sample size, median (IQR)	48 (28–102)	95 (36–205)	61.5 (56–168)	46 (26–101)
Maximum follow-up in weeks Median (IQR)	17.5 (12–26)	26 (13–26)	26 (26–273)	16 (12–26.5)
Type of diabetes, *n* (%)				
Type 1 diabetes mellitus	165 (90.7)	3	6	156
Type 2 diabetes mellitus	5 (2.8)	–	–	5
Mixed populations of type 1 and type 2 diabetes mellitus	9 (4.9)	7	–	2
Pancreatogenic diabetes	1 (0.6)	–	–	1
Cystic fibrosis-related diabetes	1 (0.6)	–	–	1
Not reported	1 (0.6)	–	–	1
Mean age in years, median (IQR)	34.8 (14–44.2)	44.5 (38.9–48.7)	45.8 (37.6–50)	32.5 (13.6–43.7)
Age category, *n* (%)				
<18 years	38 (20.9)	–	–	38
≥18 years	66 (36.3)	8	4	54

TABLE 2 (Continued)

Study characteristics	Overall	Implantable CGM devices	Implantable insulin pumps	AID systems
Mixed	60 (33.0)	1	–	59
Not reported	18 (9.9)	1	2	15
Power calculations available, *n* (%)	52 (28.6)	4	2	46
Age-specific subgroup analyses, *n* (%)	46 (25.3)	1	–	45
Sex-specific subgroup analyses, *n* (%)	23 (12.6)	–	–	23
No comparison arm, *n* (%)	114 (62.6)	8	1	105
Outcomes, *n* (%)				
HbA1c	108 (59.3)	6	3	99
Other glycemic outcomes[c]	139 (76.4)	3	2	134
Diabetes-specific end-organ damage	–	–	–	–
Safety[d]	129 (70.9)	10	5	114

Abbreviations: AID, automated insulin delivery; CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin; IQR, interquartile range; non-RIS, non-randomized interventional study; RCT, randomized clinical trial.

[a]The studies were defined as pre-market if the study completion date was before the CE-mark approval date. The studies were defined as post-market if the study completion date was after the CE-mark approval date.

[b]Hospitals, supervised environments or combined settings.

[c]Including time with sensor values within, above and below the target range.

[d]Number of studies reporting on at least one safety outcome.

Laird.[16] Absolute mean differences (MDs) were calculated. Forest plots were constructed. Heterogeneity was assessed using the I^2 statistic as follows: 0%–40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: substantial heterogeneity; 75%–100%: considerable heterogeneity.[17] Publication bias was assessed using funnel plots and Egger's test. We performed the following sensitivity analyses to test the robustness of results. (1) We performed multiple sensitivity analyses to identify sources of between-study heterogeneity. We performed subgroup analyses, evaluating the role of study setting (unsupervised outpatient setting vs. controlled environments or combined settings), RCT design (parallel vs. cross-over), geographical region (by continent), funding source (industry vs. non-industry funded), CE-mark approval of device (pre-market vs. post-market), medical device (by name), AID system function (hybrid vs. fully closed-loop systems), participants' age (children or adolescents vs. adults), and diabetes type (type 1 vs. other) on results. We further performed random-effects meta-regression to analyse age, sex, diabetes duration, and follow-up time as independent variables and effect estimates as dependent variables. (2) We evaluated the role of study quality on results by excluding studies with high risk of bias from the analyses. (3) We evaluated the role of individual studies on results by removing studies one by one from the pooled analyses. (4) We meta-analysed studies of any design that compared the outcomes before and after utilization of AID systems (i.e., pre- vs. post-intervention). Results of studies on implantable insulin pumps and implantable CGM systems could not be pooled because of clinical and methodological heterogeneity. Appendix S2 provides details of the statistical analyses.

3 | RESULTS

3.1 | Identification of relevant studies

After deduplication, we identified 5693 potentially relevant citations. After initial screening of title and abstracts, the full texts of 1519 papers were selected for detailed evaluation. After full-text assessment, a total of 182 studies were included in the systematic review (Supplemental Figure S1).

3.2 | General characteristics of the included studies

A total of eight AID systems, two implantable insulin pumps and three implantable CGM systems were identified based on the CE-mark criterion (Table 1). Of the 182 studies that were included in the systematic review, 166 were on AID systems, six were on implantable insulin pumps, and 10 were on implantable CGM systems (Table 2).

The majority of studies were performed in Europe (42%) and North America (36%), and the remainder in Australia/Oceania, Asia, South America or multiple continents. The studies were published between 2009 and 2024. With regard to funding, 27% of studies reported financial support from industry. 18% of studies were pre-market (i.e., the study was completed before the date of CE-mark approval), 67% were post-market (i.e., completed after CE-mark-approval), and the remainder did not specify study completion date. With regard to study design, 29% of studies were RCTs, 24% were non-randomized clinical trials, and 47% adopted an observational

design. Fourteen out of 48 RCTs on AID systems, two of three RCTs on implantable insulin pumps, and neither of two RCTs on implantable CGM systems were pre-market studies. In all, 92% of studies were performed in unsupervised outpatient settings, and the remainder in controlled environments or combined settings.

The median (interquartile range [IQR]) sample size was 48 (28–102) participants, and the median (IQR) study duration was 17.5 (12–26) weeks. A total of 91% of studies were performed in people with type 1 diabetes, and the remainder were conducted in mixed populations of people with type 1 and type 2 diabetes, in people with type 2 diabetes, in people with pancreatogenic diabetes or in people with cystic fibrosis-related diabetes. One study did not report on diabetes type. The median (IQR) age of patients was 34.8 (14–44.2) years, and 21% and 36% of studies, respectively, were performed in people younger or older than 18 years. Age range was not reported in 10% of studies, and 33% were performed in mixed populations of younger and older subjects, although the definitions of age range for adults and paediatric populations varied across studies. Age- and sex-specific subgroup analyses were performed in 25% and 13% of studies, respectively.

Additional information on study characteristics is provided in Supplemental Tables S1–S4 and Appendix S4. Information on patient-reported outcomes was provided in 32% of studies. Of the studies on AID systems, 72% reported on the percentage of time in auto mode (Supplemental Table S3).

A total of 37% of studies had a comparator group, comparing a CE-marked high-risk medical device with other high-risk medical devices or other treatments including standard diabetes therapy, multiple daily insulin injections with or without a glucose sensing-device, continuous subcutaneous insulin infusion with or without sensor augmentation and with or without [predictive] low-glucose suspend (Supplemental Table S1). Studies comparing different characteristics of a CE-marked high-risk medical devices (e.g., different times of use) and studies comparing different approaches (e.g., different insulin formulations, different prior treatments, or different physical activity levels) in combination with a CE-marked high-risk medical device were only considered relevant for the systematic review of safety outcomes.

3.3 | High-risk medical devices for diabetes—impact on HbA1c

3.3.1 | AID systems

Ninety-nine studies (24 RCTs, 48 observational studies, and 27 non-randomized clinical trials) evaluated the effect of AID systems on HbA1c (Table 3, Supplemental Table S5). Twenty-five studies compared AID systems with other antidiabetic treatments, of which 17 studies reported a decrease in HbA1c (ranging from −0.2 to −1.4 percentage points) and others reported no differences. A total of 92 studies evaluated differences in HbA1c before and after utilization of AID systems, of which 80 studies reported a decrease in HbA1c (ranging from −0.1 to −2.9 percentage points) and others reported no differences. Three studies performed head-to-head comparisons of AID systems with other AID systems, reporting better glycaemic control for Medtronic 780G compared with 670G, inferior glycaemic control for Medtronic 670G compared with an open-source AID system, and no differences in glycaemic control between Medtronic 780G and an open-source AID system.

Meta-analysis of 21 RCTs showed that AID utilization decreased HbA1c by 0.5 percentage points compared with control antidiabetic treatments (MD = −0.5, 95% confidence interval [CI] −0.6; −0.3; $I^2 = 85.5\%$ [Table 4, Supplemental Figure S2]). Meta-analysis of 80 studies of any design showed that HbA1c levels decreased by 0.7 percentage points after AID utilization compared with before (MD = −0.7, 95% CI −0.8; −0.5; $I^2 = 97.9\%$). Sensitivity analyses provided consistent results (Supplemental Tables S6 and S7, Supplemental Figures S3 and S4).

3.3.2 | Implantable insulin pumps

Three studies (two RCTs and one observational study) evaluated the effect of implantable insulin pumps on HbA1c, compared with other antidiabetic treatments (multiple daily injection insulin therapy, or continuous subcutaneous insulin infusion [Table 3, Supplemental Table S5]). One RCT reported a decrease in HbA1c (MD = −0.8 percentage points) and the other observed no effect. The observational study reported an association of implantable insulin pumps with higher HbA1c (MD = 0.3 percentage points).

3.3.3 | Implantable CGM systems

Six studies (one RCT, one observational study, and four non-randomized trials) evaluated the effect of implantable CGM systems on HbA1c (Table 3, Supplemental Table S5). Of these, one study comparing Eversense Glucose Sensor with intermittently scanned CGM, reported no differences in HbA1c. The other five studies compared HbA1c changes before and after implantable CGM, with three studies reporting a decrease in HbA1c after CGM (ranging from −0.30 to −0.43 percentage points), while two studies showed no differences.

3.4 | High-risk medical devices for diabetes—impact on time with sensor values in target range

3.4.1 | AID systems

A total of 133 studies (32 RCTs, 67 observational studies, and 34 non-randomized trials) evaluated the effect of AID systems on percentage of time that glucose level was in the target range of 3.9 to 10 mmol/L (TIR; Table 3, Supplemental Table S8). Thirty-six studies compared AID systems to other antidiabetic treatments, of which 35 studies reported an increase in TIR (ranging 5.9 from to 35.3 percentage points) and one study reported no differences. Out of 112 studies that evaluated differences in TIR before and after

TABLE 3 Results of the systematic review on the impact of high-risk CE-marked medical devices for glucose management[a] on efficacy outcomes.[b]

Efficacy outcomes	Total studies on an efficacy outcome (Study designs)	Studies comparing CE-marked high-risk medical devices with other antidiabetic treatments (Results)[c]	Studies comparing CE-marked high-risk medical devices with other high-risk medical devices (Results)	Studies comparing the periods before vs. after utilization of high-risk medical devices (Results)
Implantable CGM devices				
HbA1c (%)	*N* = 6 (1 RCT, 1 observational, 4 non-RIS)	*N* = 1 (1 no A)	–	*N* = 5 (3 neg A, 2 no A)
TIR (%)	*N* = 3 (2 RCTs, 1 observational)	*N* = 2 (1 pos A, 1 no A)	–	*N* = 2 (2 pos A)
TAR (%)	*N* = 3 (2 RCTs, 1 observational)	*N* = 2 (1 neg A, 1 no A)	–	*N* = 2 (2 neg A)
TBR (%)	*N* = 3 (2 RCTs, 1 observational)	*N* = 2 (2 no A)	–	*N* = 2 (1 neg A, 1 no A)
Time below 3 mmol/L (%)	*N* = 1 (1 RCT)	*N* = 1 (1 no A)	–	–
Implantable insulin pumps				
HbA1c (%)	*N* = 3 (2 RCTs, 1 observational)	*N* = 3 (1 neg A, 1 pos A, 1 no A)	–	–
TIR (%)	*N* = 2 (1 RCT, 1 observational)	*N* = 2 (1 pos A, 1 neg A)	–	–
TAR (%)	*N* = 2 (1 RCT, 1 observational)	*N* = 2 (1 neg A, 1 pos A)	–	–
TBR (%)	*N* = 2 (1 RCT, 1 observational)	*N* = 2 (2 no A)	–	–
Time below 3 mmol/L (%)	–	–	–	–
AID systems				
HbA1c (%)	*N* = 99 (24 RCTs, 48 observational, 27 non-RIS	*N* = 25 (17 neg A, 8 no A)	*N* = 3 (1 neg A, 1 pos A, 1 no A)	*N* = 92 (80 neg A, 12 no A)
TIR (%)	*N* = 133 (32 RCTs, 67 observational, 34 non-RIS)	*N* = 36 (35 pos A, 1 no A)	*N* = 5 (1 pos A, 2 neg A, 2 no A)	*N* = 112 (108 pos A, 4 no A)
TAR (%)	*N* = 103 (31 RCTs, 47 observational, 25 non-RIS)	*N* = 32 (27 neg A, 5 no A)	*N* = 4 (1 neg A, 2 pos A, 1 no A)	*N* = 85 (78 neg A, 1 pos A, 7 no A)
TBR (%)	*N* = 104 (31 RCTs, 45 observational, 28 non-RIS)	*N* = 32 (16 neg A, 1 pos A, 15 no A)	*N* = 4 (2 neg A, 2 no A)	*N* = 87 (38 neg A, 6 pos A, 43 no A)
Time below 3 mmol/L (%)	*N* = 95 (28 RCTs, 40 observational, 27 non-RIS)	*N* = 29 (9 neg A, 1 pos A, 19 no A)	*N* = 4 (3 neg A, 1 no A)	*N* = 82 (27 neg A, 5 pos A, 50 no A)

Abbreviations: AID, automated insulin delivery; CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin; pos A, positive association between the utilization of a high-risk CE-marked medical device and an efficacy outcome; neg A, negative association between the utilization of a high-risk CE-marked medical device and an efficacy outcome; no A, lack of statistically significant association between the utilization of a high-risk CE-marked medical device and an efficacy outcome; *N*, total number of studies; non-RIS, non-randomized interventional study; RCT, randomized clinical trial; TAR, time with sensor values above target range; TBR, time with sensor values below target range; Time below 3 mmol/L, time with sensor values below 3 mmol/L; TIR, time with sensor values in target range; –, no studies available.

[a]High-risk CE marked medical devices for glucose management include implantable CGM devices, implantable insulin pumps, and AID systems.

[b]Outcomes related to efficacy included metrics of glucose control, such as HbA1c (reflecting average blood glucose concentrations for the past 2–3 months); metrics calculated from plasma glucose or interstitial glucose concentrations (e.g., proportion of values within, above and below the glucose target range), and diabetes-specific end-organ damage. We found no studies investigating effects on diabetes-related end-organ damage.

[c]Other antidiabetic treatments include standard diabetes therapy, multiple daily insulin injections with or without a glucose-sensing device, continuous subcutaneous insulin infusion with or without sensor augmentation with or without (predictive) low-glucose suspend.

TABLE 4 Meta-analyses on the impact of automated insulin delivery systems on HbA1c and continuous glucose monitoring metrics.

Outcome[a]	*N*	Mean difference (95% CI)	I^2
HbA1c (%)			
RCTs[b]	21	**−0.46 (−0.59; −0.34)**	85.5%
Studies of any design[c]	80	**−0.65 (−0.75; −0.54)**	97.9%
TIR (%)			
RCTs[b]	27	**13.40 (11.13; 15.67)**	89.5%
Studies of any design[c]	94	**12.24 (11.44; 13.03)**	98.8%
TAR (%)			
RCTs[b]	26	**−11.67 (−13.87; −9.47)**	86.2%
Studies of any design[c]	73	**−9.95 (−10.56; −9.34)**	97.8%
TBR (%)			
RCTs[b]	26	**−0.82 (−1.14; −0.49)**	91%
Studies of any design[c]	73	**−0.70 (−0.81; −0.59)**	97%
Time below 3 mmol/L (%)			
RCTs[b]	23	**−0.12 (−0.19; −0.06)**	80.3%
Studies of any design[c]	69	**−0.11 (−0.14; −0.08)**	96.9%

Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; I^2, heterogeneity; *N*, total number of studies; RCT, randomized clinical trial; TAR, time with sensor values above target range; TBR, time with sensor values below target range; Time below 3 mmol/L, time with sensor values below 3 mmol/L; TIR, time with sensor values in target range.

[a]Higher values of TIR and lower values of HbA1c, TAR, TBR, and time below 3 mmol/L indicate a better glycaemic control.

[b]RCTs evaluating the effect of automated insulin delivery (AID) systems on the outcome (ie, HbA1c, time in range, time above range, time below range, time below 3 mmol/L). The comparator (Reference) includes any antidiabetic treatment other than high-risk medical devices.

[c]Studies of any design comparing the outcome (ie, HbA1c, time in range, time above range, time below range, time below 3 mmol/L) before (Reference) vs. after utilization of AID systems (i.e., pre-post intervention).

utilization of AID systems, 108 studies reported an increase in TIR percentage (ranging from 4 to 38.9 percentage points), while the remaining studies reported no differences after implementing AID systems. Five studies performed head-to-head comparisons of AID systems with other AID systems. Of these, three studies reported an increase in TIR for Medtronic 780G compared with 670G, for Medtronic 780G compared with Tandem Control-IQ, and for an open-source AID system compared with Medtronic 670G. The remaining two studies reported no differences between Medtronic 770G and 670G, and no differences between Medtronic 780G and an open-source AID system.

Meta-analysis of 27 RCTs showed that AID utilization increased TIR by 13.4 percentage points compared with other antidiabetic treatments (MD = 13.4, 95% CI 11.1; 15.7; $I^2 = 89.5\%$ [Table 4, Supplemental Figure S5]). Meta-analysis of 94 studies of any design showed that TIR percentage increased by 12.2 percentage points after AID utilization compared with before (MD = 12.4, 95% CI 11.4; 13; $I^2 = 98.8\%$). Sensitivity analyses provided consistent results (Supplemental Tables S6 and S7, Supplemental Figures S3 and S4).

3.4.2 | Implantable insulin pumps

Two studies (one RCT, one observational study) evaluated the effect of implantable insulin pumps on TIR, compared to other antidiabetic treatments (multiple daily injection insulin therapy, or continuous subcutaneous insulin infusion; Table 3, Supplemental Table S8). The RCT reported an increase in TIR (MD = 10.9 percentage points), while the observational study reported a decrease in TIR (MD = −6.9 percentage points).

3.4.3 | Implantable CGM systems

Three studies (two RCTs and one observational study) evaluated the effect of implantable CGM systems on TIR (Table 3, Supplemental Table S8). Of these, one study showed no difference in TIR when comparing Eversense Glucose Sensor with intermittently scanned CGM. One study reported that the Eversense Glucose Sensor was associated with an increase in TIR compared with Dexcom G5 (MD = 4.15 percentage points). Two studies reported an increase in TIR after implantable CGM utilization compared to before (ranging from 3.8 to 5.3 percentage points).

3.5 | High-risk medical devices for diabetes—impact on time with sensor values above target range

3.5.1 | AID systems

A total of 103 studies (31 RCTs, 47 observational studies, and 25 non-randomized trials) evaluated the effect of AID systems on percentage of time that glucose level was above 10 mmol/L (TAR; Table 3, Supplemental Table S9). Thirty-two studies compared AID systems to other antidiabetic treatments, of which 27 studies reported a decrease in TAR

(ranging from −35.2 to −5 percentage points) and five studies reported no differences. Out of 85 studies that evaluated differences in TAR before and after utilization of AID systems, 78 studies reported a decrease in TAR (ranging from −37.3 to −2.9 percentage points), one study reported an increase in TAR (MD = 3 percentage points), while the remaining studies reported no differences after implementing AID systems. Four studies performed head-to-head comparisons of AID systems with other AID systems, of which three studies reported a decrease in TAR for Medtronic 780G compared with 670G, for Medtronic 780G compared with Tandem Control-IQ, and for an open-source AID system compared with Medtronic 670G, and one study reported no difference between Medtronic 770G and 670G.

Meta-analysis of 26 RCTs showed that AID utilization decreased TAR by 11.7 percentage points compared with other antidiabetic treatments (MD = −11.7, [95% CI −13.9; −9.5]; I^2 = 86.2% [Table 4, Supplemental Figure S6]). Meta-analysis of 73 studies of any design showed that TAR percentage decreased by 9.9 percentage points after AID utilization compared with before (MD = −9.9 [95% CI −10.6; −9.3]; I^2 = 97.8%). Sensitivity analyses provided consistent results (Supplemental Tables S6 and S7, Supplemental Figures S3 and S4).

3.5.2 | Implantable insulin pumps

Two studies (one RCT, one observational study) evaluated the effect of implantable insulin pumps on TAR, compared to other antidiabetic treatments (multiple daily injection insulin therapy, or continuous subcutaneous insulin infusion). The RCT reported a decrease in TAR (MD = −8.9 percentage points), while the observational study reported an increase in TAR (MD = 9.3 percentage points; Table 3, Supplemental Table S9).

3.5.3 | Implantable CGM systems

Three studies (two RCTs and one observational study) evaluated the effect of implantable CGM systems on TAR (Table 3, Supplemental Table S9). Of these, one study showed no differences in TAR when comparing Eversense Glucose Sensor with intermittently scanned CGM. One study reported that the Eversense Glucose Sensor was associated with a decrease in TAR compared with Dexcom G5 (MD = −4.5 percentage points). Two studies reported a decrease in TAR after implantable CGM utilization compared to before (ranging from −2.2 to −6 percentage points).

3.6 | High-risk medical devices for diabetes—impact on time with sensor values below target range

3.6.1 | AID systems

A total of 104 studies (31 RCTs, 45 observational studies, and 28 non-randomized trials) evaluated the effect of AID systems on percentage of time that glucose level was below 3 mmol/L (TBR; Table 3, Supplemental Table S10). Thirty-two studies compared AID systems to other antidiabetic treatments, of which 16 studies reported a decrease in TBR (ranging from −3.7 to −0.4 percentage points), one study reported an increase in TBR and the remaining studies reported no differences. Out of 87 studies that evaluated differences in TBR before and after utilization of AID systems, 38 studies reported a decrease in TBR (ranging from −6.6 to −0.2 percentage points), six studies reported an increase in TBR (ranging from 0.2 to 1.4 percentage points), while the remaining studies reported no differences after implementing AID systems. Four studies performed head-to-head comparisons of AID systems with other AID systems, of which two studies reported a decrease in TBR for Tandem Control-IQ compared with Medtronic 780G, for Medtronic 670G compared with an open-source AID system. One study reported no difference between Medtronic 770G and 670G, and one study reported no difference between Medtronic 780G and 670G.

Meta-analysis of 26 RCTs showed that AID utilization decreased TBR by 0.82 percentage points compared with other antidiabetic treatments (MD = −0.8, 95% CI −1.1; −0.5; I^2 = 91% [Table 4, Supplemental Figure S7]). Meta-analysis of 73 studies of any design showed that TBR percentage decreased by 0.70 percentage points after AID utilization compared with before (MD = −0.7, 95% CI −0.8; −0.6; I^2 = 97%). Sensitivity analyses provided consistent results (Supplemental Tables S6 and S7, Supplemental Figures S3 and S4).

3.6.2 | Implantable insulin pumps

Two studies (one RCT, one observational study) evaluated the effect of implantable insulin pumps on TBR, compared to other antidiabetic treatments (multiple daily injection insulin therapy, or continuous subcutaneous insulin infusion), reporting no changes in TBR (Table 3, Supplemental Table S10).

3.6.3 | Implantable CGM systems

Three studies (two RCTs and one observational study) evaluated the effect of implantable CGM systems on TBR (Table 3, Supplemental Table S10). Of these, two studies showed no differences in TBR when comparing Eversense Glucose Sensor with intermittently scanned CGM or Dexcom G5, respectively. One study reported a decrease in TBR after implantable CGM utilization compared to before (MD = −0.7 percentage points), while another study reported no differences.

Table 3, Table 4, Supplemental Table S11 and Supplemental Figure S8 provide additional information on the effect of high-risk medical devices for diabetes on time below 3 mmol/L.

3.7 | High-risk medical devices for diabetes—impact on diabetes-related end-organ damage

No studies investigated effects on diabetes-related end-organ damage.

3.8 | High-risk medical devices for diabetes—impact on safety outcomes

Table 5 and Supplemental Table S12 summarize the results of 129 studies reporting on at least one safety outcome, including diabetic ketoacidosis (103 studies, 80%), severe hypoglycaemia (114 studies, 88%), or other device-related SAEs (59 studies, 46%). Thirty studies (23%) reported on device deficiencies, but none specified whether they had SAE potential. Of the 129 studies, 59 had a comparison arm (Supplemental Table S12a). The overall frequencies of diabetic ketoacidosis or severe hypoglycaemia were low and similar in the two arms, but only one study evaluated if there were significant differences (Liebl et al). The frequency of device-related SAEs was also low. Of the 129 studies, 69 described safety outcomes before and after the intervention (Supplemental Table S12b). The overall occurrence of safety events during follow-up was low.

3.9 | Quality assessment

Of 53 RCTs, 18 had low risk of bias, 30 had some concerns for bias, and five had high risk of bias (Figure 1, Supplemental Table S13). Of 86 observational studies, 60 had low, 0 had moderate and 26 had high risk of bias. Of 43 non-randomized interventional studies, 32 had low, 11 had moderate and 0 had high risk of bias.

3.10 | Publication bias assessment

Supplemental Figure S9 depicts the funnel plots for detection of publication bias. Egger's regression tests indicated significant funnel plot asymmetry for RCTs. Nevertheless, the results of our meta-analyses remained consistent after use of the trim-and-fill method and after restricting the analyses to studies within the pseudo 95% CI of the funnel plots. Egger's regression tests did not show significant funnel plot asymmetry for studies of any design that compared the efficacy outcomes before and after utilization of AID systems (i.e., pre- vs. post-intervention).

4 | DISCUSSION

4.1 | Summary of main findings

This systematic review and meta-analysis, conducted within the framework of the CORE-MD project, comprehensively evaluated

TABLE 5 Results of the systematic review on the impact of high-risk CE-marked medical devices on safety outcomes.[a]

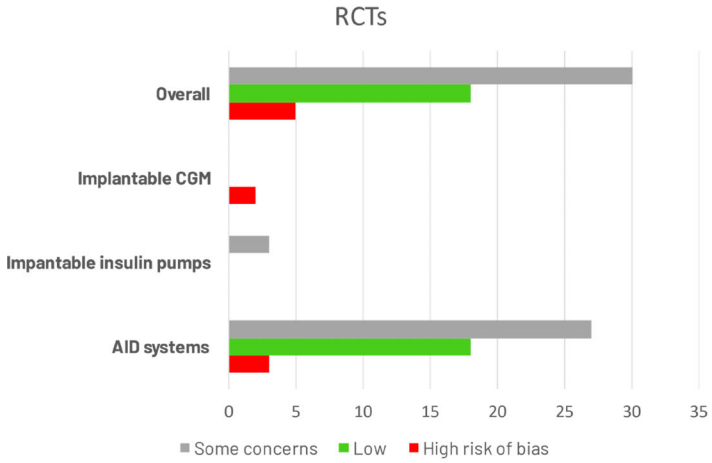
Device class	Number of studies reporting on at least one safety outcome	Safety outcomes			
		Diabetic ketoacidosis	Severe hypoglycaemia	Other device-related SAEs[b]	Device deficiency with SAE potential[c]
Implantable CGM devices	10	$n = 1$ (1%)	$n = 1$ (0%)	$n = 7$ (0%) $n = 1$ (1%)	NR
Implantable insulin pumps	5	$n = 1$ (9 episodes in 56 participants)	$n = 1$ (8%) $n = 1$ (14%) $n = 1$ (IR, 0.35 PY)	NR	NR
AID systems	114	$n = 84$ (0%) $n = 11$ (0.1–10%) $n = 1$ (2 episodes in 191 participants) $n = 1$ (9 episodes in 56 participants) $n = 1$ (2 episodes in 49 participants) $n = 1$ (2 episodes in 20 participants; IR, 0.4 PY) $n = 1$ (5 episodes in 15 participants; IR, 0.72 PY) $n = 1$ (3 episodes in 20 participants; IR, 0.15 PY)	$n = 87$ (0%) $n = 13$ (0.1–10%) $n = 5$ (10–20%) $n = 1$ (25%) $n = 1$ (2 episodes in 68 participants) $n = 1$ (5 episodes in 63 participants) $n = 1$ (11 episodes in 135 participants) $n = 1$ (IR, 0.09 PY)	$n = 45$ (0%) $n = 5$ (0.1–10%) $n = 1$ (5 episodes in 61 participants)	NR

Abbreviations: AID, automated insulin delivery; CGM, continuous glucose monitoring; IR, incidence rate; NR, not reported; PY, person-years; SAE, serious adverse event.

[a]This table indicates the number of studies that report the percentage of events or the number of episodes or the incidence rate in the intervention arm (provided in brackets).

[b]A device-related SAE is defined as any SAE that has a causal relationship with the investigational device or where such causal relationship is reasonably possible. A SAE is defined as any adverse event that led to death, serious deterioration in the health of the patient requiring medical assistance including emergency medical services and/or hospitalization.

[c]A device deficiency with a SAE potential is defined as any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.



Risk of bias	Low	Some concerns	High
RCTs			
Overall (*n*)	18	30	5
Implantable CGM (*n*)	0	0	2
Implantable insulin pumps (*n*)	0	3	0
AID systems (*n*)	18	27	3
Observational studies			
Overall (*n*)	60	0	26
Implantable CGM (*n*)	2	0	1
Implantable insulin pumps (*n*)	1	0	2
AID systems (*n*)	57	0	23
Non-RIS			
Overall (*n*)	32	11	0
Implantable CGM (*n*)	3	2	0
Implantable insulin pumps (*n*)	0	0	0
AID systems (*n*)	29	9	0

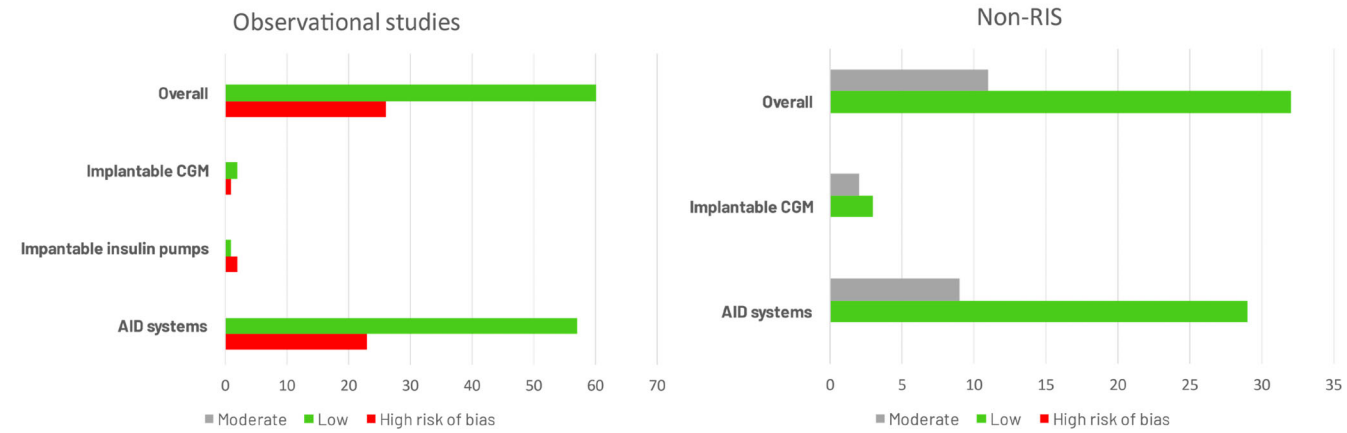


FIGURE 1 Quality assessment of randomized clinical trials (RCTs), observational studies, and non-randomized interventional studies (non-RIS). The quality of evidence of RCTs was assessed using version 2 of the Cochrane Risk of Bias Assessment Tool (low risk, some concerns, or high risk of bias). The quality of evidence of observational studies was assessed using the Newcastle–Ottawa Scale (low, moderate, or high risk of bias). The quality of evidence of non-randomized interventional studies with no control group was assessed using the validated National Institute of Health assessment tool for before–after (pre–post) studies without control group (low, moderate, or high risk of bias). AID, automated insulin delivery; CGM, continuous glucose monitoring; *n*, number of studies.

the efficacy and safety of high-risk medical devices licensed in Europe for glucose control in people with diabetes. Overall, our findings indicate a positive benefit/risk balance through the use of these devices for diabetes management. AID systems, in particular, consistently decreased HbA1c, increased TIR, and decreased TAR, TBR, and time with sensor values below 3 mmol/L, without substantial increases in the occurrence of severe hypoglycaemia, diabetic ketoacidosis, or other device-related SAEs. The occurrence of device deficiencies with SAE potential, a safety endpoint that is specified by regulatory standards, were not reported. The utilization of implantable insulin pumps and CGM systems also led to favourable glycaemic outcomes, although the number of eligible studies for these devices was lower than for AID systems. Efficacy evaluation was largely confined to glucose control, with none of studies reporting on diabetes-related end-organ damage. The overall quality of studies varied from high to moderate to low. Totals of 18% and 67% of studies were pre- and post-market, respectively.

4.2 | Comparing our results with previous studies

The efficacy of AID systems in improving glycaemic control is consistent with prior research.[18–22] Previous systematic reviews and meta-analyses of RCTs in outpatients with type 1 diabetes reported significant reductions in HbA1c and TIR with the use of AID systems compared with insulin-based treatments.[18–22] While further updating and solidifying this evidence, our systematic review and meta-analysis focuses on investigations of high-risk medical devices conducted before and after CE marking, thereby providing insights into current regulatory practices in Europe and highlighting the need for more

guidance (i.e., standardization and transparency). Compared to the previous systematic reviews and meta-analyses, we used broader eligibility criteria, including a wider range of medical devices (i.e., not only AID systems, but also implantable insulin pumps and implantable CGM systems), with no restrictions on population characteristics, and no restrictions on study design, which enabled us to capture a larger number of eligible studies and increase generalizability of findings. In order to provide a balanced overview of the beneficial and deleterious effects of high-risk medical devices, we further extended the current knowledge by performing a systematic review on the safety outcomes.

4.3 | Sensitivity analyses

We evaluated the potential influence of multiple factors (e.g., study design, type of intervention, study population) on our results by performing multiple subgroup and meta-regression analyses on the efficacy of AID systems. Our data indicate that the beneficial effects of AID systems on HbA1c and CGM metrics are robust irrespective of whether the study was financially supported by industry and irrespective of whether the device was CE-marked at the time of the study. Similarly, our results remained consistent across different RCT designs (parallel vs. cross-over), durations of follow-up time, and study settings (unsupervised outpatient settings vs. controlled environments). Our data further indicate the glycaemic efficacy of all eligible AID systems, including both hybrid and fully closed-loop systems. Lastly, our data indicate the efficacy of AID systems across people of different ages, forms of diabetes, and geographical locations. Future research should be focused on identifying specific populations that may benefit the most from these devices.

4.4 | Safety outcomes

Several aspects related to our results on the safety outcomes warrant discussion. Firstly, the overall occurrence of safety events, including diabetic ketoacidosis, severe hypoglycaemia, and other device-related severe adverse events was low. However, the duration of studies was relatively short, and the long-term implications of high-risk medical devices on safety events should be investigated more extensively over adequate follow-up times. Post-market surveillance in registries with comprehensive end-user criteria (>95% of eligible users) may address this need. In the framework of new EU rules for medical devices, safety reporting in the EUDAMED database will be mandatory by 2026.

Secondly, no studies reported on device deficiencies with serious adverse potential, which is a requirement in safety reporting guidelines. The lack of reporting can be explained by the hypothetical nature of this safety event category. The reported frequency of experienced device deficiencies was moderate to low. Yet, in the absence of specific guidance and standards tailored to clinical context, the identification of device deficiencies that require reporting currently remains at the discretion of the investigators.

Thirdly, the terminology and definitions of safety events across studies were heterogenous. The method of reporting of safety events also varied, with some studies reporting on a single safety outcome and others reporting on multiple safety outcomes, and with some studies reporting the number of episodes and others reporting the number of participants experiencing safety events. In view of these considerations, there is a need for a standardized approach to reporting safety outcomes. This can be achieved via the development of guidance on reporting, which would lead to the utilization of a unified terminology of safety events, comprehensive evaluation and detailed reporting of safety events across studies.

Lastly, the occurrence of certain safety events, such as severe hypoglycaemia and diabetic ketoacidosis, was generally low, which made it difficult to assess potential statistical differences between study arms. This highlights the need to address statistical considerations in the analysis of safety data, including choosing appropriate methodologies to detect relevant but rare safety signals.

4.5 | Additional implications of our findings

The increasing number of studies showing substantial improvements in HbA1c and TIR due to AID systems indicate a major shift in diabetes management, emphasizing the role of technological innovation in improving patients' health. This underscores the importance of continued research and development in this area.

For several devices included in our systematic review, pre-market investigations were characterized by evidence only from observational studies and/or only one RCT. This contrasts with the approval process for new drugs, which is usually supported by evidence from large RCTs on efficacy and safety. However, it is also likely that specific algorithms used for current CE-marked devices were tested previously in other devices differing from those used in the CE-marked approved system. Our study thus highlights the need for a more comprehensive and transparent regulatory framework, particularly in the EU. The lack of complete data on CE-marked devices, as evidenced by our reliance on multiple sources for information, points to gaps in the current system. Strengthening the EUDAMED database and mandating registration can aid in better monitoring and evaluation of current and future devices. Additionally, the variability of results across studies of similar methodology raises questions about patient-specific factors (physiology and behaviour), influencing device efficacy and safety. This underlines the necessity for personalized approaches in diabetes care, considering individual patient needs and preferences.

Future studies investigating the efficacy and/or safety of high-risk medical devices should comply with standards that include criteria for study design and outcomes (e.g., performance and safety outcomes). While there is a recently published consensus statement on CGM metrics for clinical trials (in addition to HbA1c),[11] no such consensus exists for safety outcomes. We suggest evaluating safety based on the incidence of severe (Level 3) hypoglycaemia according to the International Hypoglycemia Study Group taxonomy,[23] diabetic ketoacidosis, other device-related SAEs, and device deficiencies with SAE potential. Device usage time should also be reported as a relevant

usability outcome for overall interpretation of results along with patient-reported outcome studies.[24] Long-term risk/benefit and cost-effectiveness analyses require further evaluation of target end-organ damage (e.g., composite kidney and cardiovascular endpoints). In the future, alignment of studies with standardized outcome definitions requires the development of further consensus statements by qualified and balanced committees of experts, coordinated by international societies.

4.6 | Strengths and limitations

Major strengths of our systematic review include the considerable number of included studies ($n = 182$) and the balanced overview of the efficacy and safety of high-risk medical devices, which received CE marking for diabetes management. The efficacy and safety outcomes were evaluated in a comprehensive manner. Furthermore, our systematic review provides extensive and detailed information on the characteristics of eligible studies. We identified both pre- and post-market studies, thus increasing the transparency of reporting. We included a wide range of study designs, which enabled the comparison between experimental and real-world evidence. The inclusion of people of different ages and various geographical locations increased the generalizability of findings.

The systematic review was based on the Cochrane Handbook and PRISMA guidelines. Quality of evidence was evaluated in accordance with study designs. We also assessed the possibility of publication bias. The large number of studies allowed us to perform detailed subgroup analyses, which showed consistent findings. Nevertheless, our results are limited by the quality of the included studies; the studies were generally characterized by relatively small sample sizes, short follow-up and methodological heterogeneity. Furthermore, individuals with higher socioeconomic status may have greater access to and support in using medical devices such as AID systems. Therefore, we cannot rule out the possibility that individuals from less advantaged backgrounds are underrepresented in the existing interventional and observational studies. Lastly, a medical device may be refined over time until it eventually evolves into a mature device that is commercially available. However, our systematic review and meta-analysis selected only the studies on prespecified CE-marked medical devices for feasibility reasons (challenge of linking early prototype research with more mature, ready-for-commercialization devices) and to allow for transferability of knowledge to current clinical practice.

5 | CONCLUSIONS

Our systematic review and meta-analysis indicates the efficacy and safety of high-risk medical devices for glucose monitoring and insulin dosing, with AID systems providing the largest contribution to the evidence. The improvements in HbA1c and TIR with comparably low incidence of safety events are notable, indicating a favourable risk/benefit balance and consequently potential beneficial effects on diabetes-related end-organ damage. The varying degrees of clinical efficacy across different devices, and the heterogenous way of reporting on design, outcomes and technical device performance highlight the need for developing standards for future pre- and post-market investigations, thereby improving study comparability and transparency of findings.

AUTHOR CONTRIBUTIONS

Conceptualization and design: Arjola Bano and Lia Bally. Search strategy: Arjola Bano, Tania Rivero and Lia Bally. Abstract screening: Arjola Bano, Juri Künzler and Faina Wehrli. Data extraction: Arjola Bano, Juri Künzler, Adea Llane and Angelica Valz Gris. Quality assessment: Arjola Bano, Faina Wehrli, Lum Kastrati, Adea Llane and Angelica Valz Gris. Statistical analyses and visualization: Arjola Bano. Original draft preparation: Arjola Bano. Critical revision and editing of the draft article: Arjola Bano, Juri Künzler, Faina Wehrli, Lum Kastrati, Tania Rivero, Adea Llane, Angelica Valz Gris, Alan G. Fraser, Christoph Stettler, Roman Hovorka, Markus Laimer and Lia Bally. Supervision: Arjola Bano, Alan G. Fraser, Markus Laimer and Lia Bally.

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CONFLICT OF INTEREST STATEMENT

Roman Hovorka reports having received speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving licence fees from BBraun, and being a director at CamDiab. Lia Bally reports having received speaker honoraria and advisory board fees from Dexcom, Ypsomed, Roche Diabetes Care, Sanofi and Novonordisk, and support from Dexcom, Novonordisk and Ypsomed for investigator-initiated research. All other authors declare no competing interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15849.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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