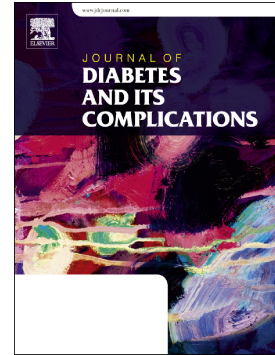


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**Detection of asymptomatic drug-induced hypoglycemia using continuous glucose monitoring in older people – systematic review**

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**Abstract***Aim*

We conducted a systematic review of the use of continuous glucose monitoring (CGM) in older patients, in order to consolidate the growing evidence base in this area.

*Methods*

Our protocol was registered on PROSPERO (CRD42017068523).

We searched SCI Web of Science, Ovid SP MEDLINE and EMBASE from January 2010 to June 2017 for observational studies and randomized controlled trial of CGM in older patients (mean age 65 or older) with diabetes. We excluded studies that involved only hospitalized patients. Two reviewers independently extracted data blood sugar values (in particular, hypoglycemic episodes) captured with the use of CGM. We also assessed adverse events and acceptability of CGM.

*Results*

After screening 901 abstracts, we included nine studies with a total of 989 older patients with diabetes.

The CGM studies reveal that hypoglycemic episodes were occurring in a sizeable proportion (28-65%) of participants. Most (80-100%) of these episodes were asymptomatic, with some patients spending nearly two hours per day in the hypoglycemic range. Older people with diabetes found CGM acceptable and experienced improved health-related well-being.

*Conclusion*

CGM frequently picks up asymptomatic hypoglycemic episodes in older patients with diabetes. Users of CGM report improved well-being, and reduction of diabetes-related stress.

**Keywords:** hypoglycemia; older people; continuous glucose monitoring

## 1 Introduction

Self-management of diabetes mellitus in older people with multiple comorbidities (including cognitive impairment) is challenging, because the extent of harm from hypoglycemia, and the optimal means of monitoring blood glucose in this population, is not known. Current strategies of monitoring (such as glycated hemoglobin or intermittent finger-prick testing) may not be entirely appropriate for older patients who face difficulties in recognizing and managing changes in blood sugars

Recent research has demonstrated that routine self-monitoring of blood glucose (SMBG) in patients with non-insulin treated type 2 diabetes mellitus does not significantly improve Hemoglobin A1C (HbA1c) level or health-related quality of life (1) (2). Young et al conducted a pragmatic open-label randomized trial of 450 patients in 15 primary care practices in North Carolina. Three SMBG approaches were compared: no SMBG, once-daily SMBG and once-daily SMBG with enhanced patient feedback. No clinically or statistically differences at one year in glycemic control or health-related quality of life were observed between those who did or did not perform SMBG (1).

Malanda et al. conducted a Cochrane Review in 2012 that assessed the effects of 12 randomized controlled trials of SMBG in patients with type 2 diabetes who were non-insulin users. The reviewers concluded that when diabetes duration is over one year, the overall effect of SMBG on glycemic control is small up to six months after initiation and subsides after 12 months. The reviewers could not find evidence that SMBG affects health-related quality of life or patient satisfaction (2).

However, existing research has focused on markers of long-term efficacy or benefit, whereas for older people, the threat of hypoglycemia may be a far more immediate and pressing concern. Recent evidence from Asia shows a sharp rise in emergency admission for hypoglycemia – for instance, over a ten-year period, older people in Korea were found to have a 10-fold increased risk of hypoglycemic episodes needing hospital admission (3) (4). A study in England found that one Ambulance Trust had 523 call outs for severe hypoglycemia

(mainly in older people) over a 3-month period, with projected costs exceeding £235,000 per year (5).

Recent advances in continuous glucose monitoring (CGM) technology may uncover the true extent of (otherwise undetected) hypoglycemia. An observational study by Pazos et al in 2015 enrolled patients with type 2 diabetes who were > 60 years of age, and concluded that CGM was useful because it succeeded in detecting an almost five-fold higher rate of hypoglycemic events than through SMBG.(6). It is becoming clear that new approaches or changes in mindset are needed when formulating monitoring strategies for older patients, aimed towards measuring harm from hypoglycemia rather than efficacy targets. Hence, we have undertaken a systematic review on the role of CGM in older people, with specific focus on ascertainment of asymptomatic hypoglycemia.

## 2 Methods

Our protocol was registered on PROSPERO (CRD42017068523).

### 2.1 Study selection criteria

We included observational studies and randomized controlled trials (RCT). Population of interest was older people, mean age >65 years. Studies based solely on inpatients or laboratory settings were excluded.

### 2.2 Search Strategy

We searched three electronic databases - Web of Science, Ovid SP MEDLINE and EMBASE from January 2010 to June 2017.

No searches were conducted on unpublished or grey literature. Only human studies were included in the search.

The search strategy included terms related to the intervention (continuous glucose monitoring) and the population (older adults):

(Aged OR "older adult" OR "older adults" OR elderly OR geriatric OR veteran? OR senior?)

AND

(continuous-glucose-monitoring or CGM)

We also conducted a manual search by reviewing the reference lists of included studies and published systematic reviews on the same topic. The searches were also updated automatically on a monthly basis through electronic notifications from Pubmed.

### 2.3 Study Selection and Data Extraction

Two reviewers (YKL and KM) independently screened titles and abstracts to remove those that clearly did not fulfil selection criteria. Both reviewers then proceeded to check full-text versions of articles that were either of uncertain suitability or were judged as potentially relevant. Data extraction similarly involved two independent reviewers, with subsequent discussion to reach consensus.

We extracted the following information onto a spreadsheet: study design, geographical location, sample size, mean age, diabetes duration, model/make of CGM, selection of patients, loss to follow-up, missing data, selective reporting, summary statistics of blood sugar values captured, definition and number of hypoglycemic episodes captured, adverse events, acceptability and adherence (please refer to Appendix B Tables B.1 and B.2).

### 2.4 Quality assessment

Two reviewers assessed key parameters, including selection of patients, loss to follow-up, missing data, selective reporting and analysis.

### 2.5 Data synthesis/Analysis

We aimed to perform meta-analysis if there was sufficient quantitative data and similarity in the reported outcome measures. Assessment of statistical heterogeneity would be through the  $I^2$  statistic. We aimed to assess publication bias by examining funnel plots, if there were more than 10 included studies for a particular outcome, and there was no evidence of

significant heterogeneity. Where studies were too heterogeneous to be pooled, a narrative analysis of the data would be undertaken.

### 3 Results

After de-duplication, we screened 901 citations and one citation from automated notification. We included nine studies. (see Appendix A Figure A.1 PRISMA flow chart) (7) (8, 9) (10-13) (14) (15).

The included studies had a total of 989 participants (sample size 22 to 285) with a mean age of 70 years. Geographical locations were diverse and included North America, Japan, Canada, Germany and the Netherlands.

#### 3.1 Risk of Bias of Included Studies and Selective Outcome Reporting

There was a mix of types of studies, including RCT, retrospective health record reviews, cross-sectional studies, pilot study and mixed-method study.

Most of the studies did not provide sufficient information on blinding of assessors and participants, drop-out rates, missing data and how missing data were addressed. Only three studies employed blinding of the device readings (15) (9) (13). In addition, there is considerable variation in the definition of hypoglycemia amongst the included studies.

#### 3.2 Evidence Synthesis

The nine included studies did not have sufficient quantitative data and similarity in the reported outcome measures for us to pool the data in a meta-analysis.

We have therefore carried out a narrative synthesis under the following headings:

- Capture of hypoglycemia
- CGM satisfaction
- Association of adverse events with hypoglycemia

- Pre-and post CGM outcomes

### *Capture of hypoglycemia*

Four studies report on the number of participants who had hypoglycemic episodes recorded through blinded CGM (14) (9) (10) (13).

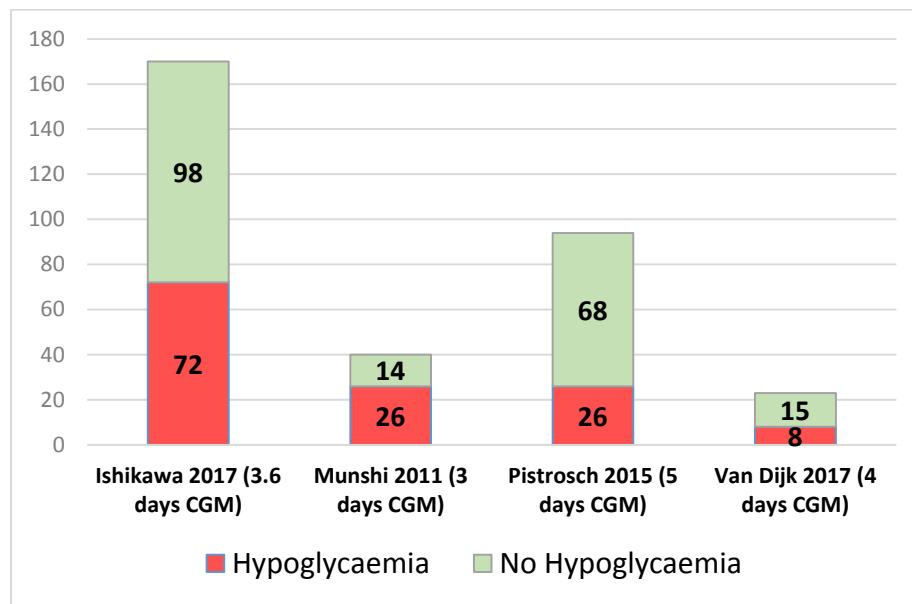
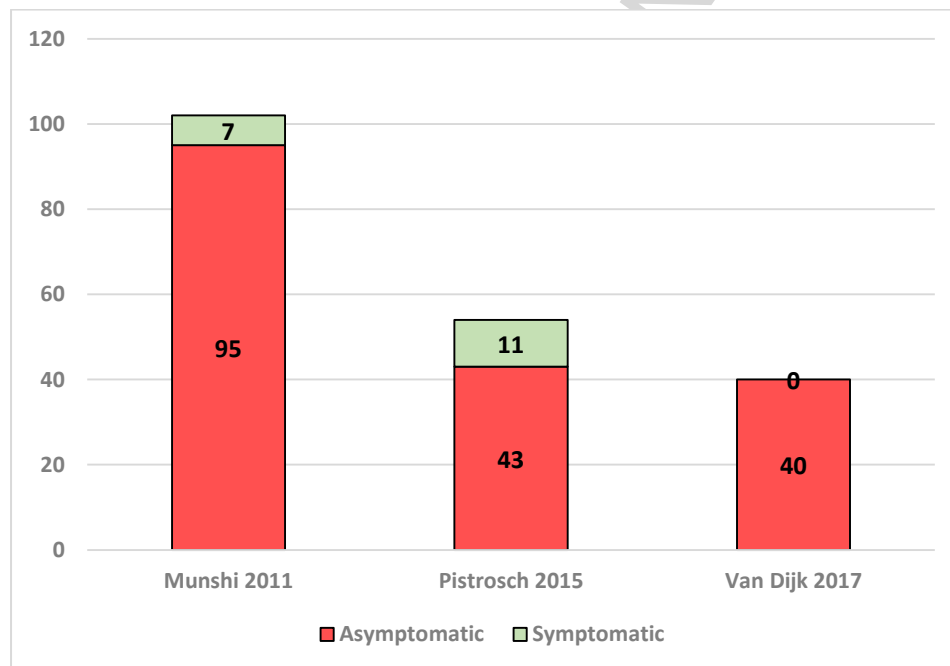
Figure 1(a) depicts the number of patients with and without hypoglycemia.

The proportion of participants affected by at least one or more hypoglycemic event varied between 28%-65%. This variation may have stemmed from differences in patient characteristics, nature of drug therapy and duration of monitoring (ranged from 3 to 5 days), nevertheless, the important unifying features of all of these studies is that CGM has demonstrated that a substantial proportion of older people are affected by hypoglycemic events.

We extracted data from three studies regarding the symptomatic or asymptomatic nature of the hypoglycemic episodes (9, 10) (13). Figure 1(b) illustrates number of hypoglycemic events with and without symptoms. All three studies used blinded CGM.

It is striking that between 80-100% of hypoglycemic events were asymptomatic and arguably most if not all of these would have gone unnoticed had it not been for the use of CGM at that particular point in time.

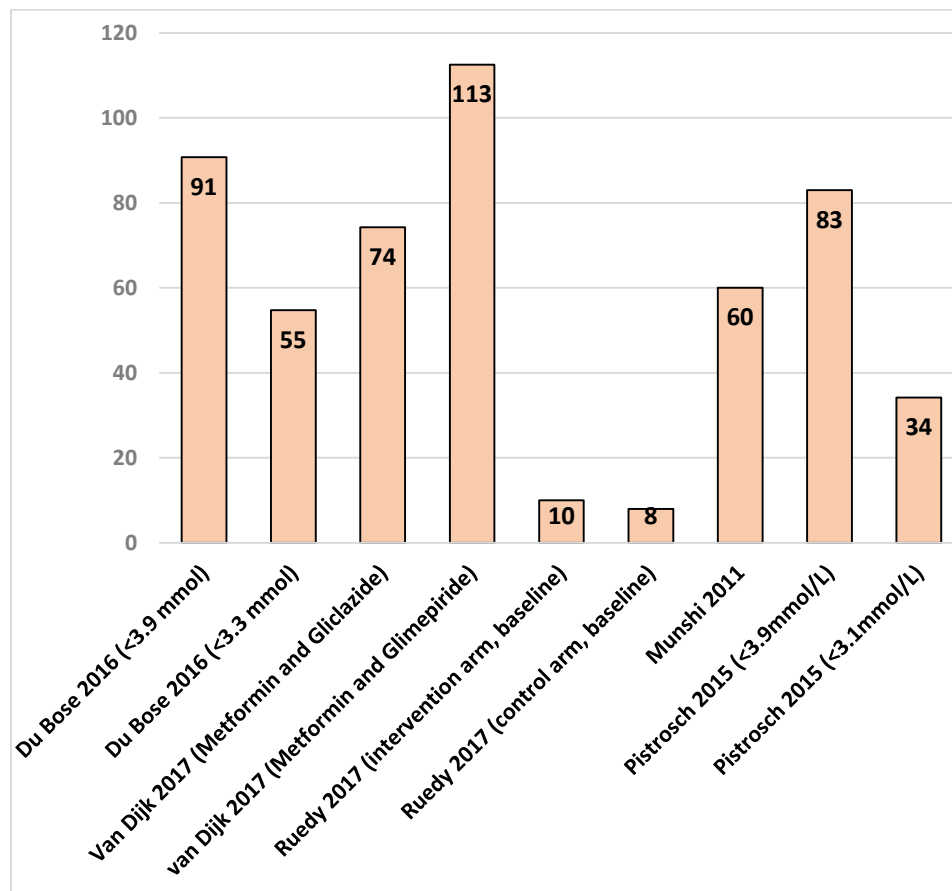


**Figure 1(a) Number of patients with and without hypoglycemia (blinded CGM)****Figure 1(b) Number of hypoglycemic events, with and without symptoms**

Finally, we estimated the length of time participants spent in the hypoglycemic range in minutes per day (see Figure 2) (15) (12, 13) (9) (10).

Participants in the observational studies spent between 34-112 minutes per day in the hypoglycemic range, whereas the baseline blinded CGM in the randomized trial by Ruedy et al. found that participants spent only between 8-10 minutes in the hypoglycemic range.

There are a number of reasons why the RCT data are outliers. The investigators conducted a post-hoc analysis of older participants in the multi-centre DIAMOND RCT comparing CGM versus self-monitoring (16). Participants all had to have a stable diabetes regime for three months prior to study entry, and were performing self-monitoring three or more times daily, with no history of recurrent hypoglycemia (16). Co-morbidities such as recent cardiovascular disease, significant heart failure, conditions resulting in physical or cognitive decline, and renal impairment were listed as exclusion criteria. The participants selected for the DIAMOND trial were not frail older people with multiple co-morbidities and possible cognitive impairment. Instead, the participants were likely to have good hypoglycemic awareness and ability to correct low blood sugars more quickly than those the frail older participants in van Dijk's study where all of the hypoglycemic episodes were asymptomatic (13).

**Figure 2 Minutes per day in the hypoglycemic range (blinded CGM)**

### CGM satisfaction

CGM satisfaction was assessed in two studies where users were not blinded to the functions of the device (8) (12). Litchman et al's mixed-methods study, used convenience sample of older adults with type 1 diabetes who completed one of two online surveys about CGM. Emerging themes were that CGM use facilitates feelings of safety by preventing hypoglycemia and improves well-being. CGM users felt that they were able to function better in their daily activities and that the device could assist in prolonging life by preventing injury and complication (8).

In Ruedy et al's study, CGM users (n=60) were asked to complete a CGM Satisfaction Survey at the 24-week follow-up. Overall satisfaction was high with mean score of 4.2 (range of scores 1-5), with mean scores of 4.3 on the Benefits subscale and 1.8 on the Hassles subscale, indicating that the perceived benefits outweighed the perceived hassles (12).

*Adverse events*

Three studies reported on adverse events, such as Emergency Department (ED) visits (11), falls, inability to operate a vehicle in the last year (8) and ventricular arrhythmias (10). It is important to note that at this juncture, we cannot draw any conclusions regarding causality between the hypoglycemic episodes and adverse events.

Litchman et al asked participants to complete an online survey which included a question on whether hospitalization had occurred in relation to a participant's diabetes since they had started using CGM, which was compared to hospitalization on non-CGM users. The results of that particular question are not reported. However, CGM users (n=11) reported 0 severe hypoglycemic episodes resulting in a fall or inability to operate a vehicle in the last year, compared to 6 non-CGM users (55%) (8).

Pistrosch et al looked at the occurrence of ventricular arrhythmias in type 2 diabetes patients who had hypoglycemic events. In their study, they observed that 13 out of 26 patients in the hypoglycemic group experienced ventricular arrhythmias, compared to 11 out of 68 participants in the non-hypoglycemic group (10).

*Adverse events pre- and post-CGM*

Polonsky et al reported reduction of 5.3% of hospitalization in CGM users comparing hospitalization six months before starting CGM and over the past six months. This reduction of hospitalization was a within-group comparison (11). There was no reduction in hospitalization in the non-CGM users in the same period. In addition, there was a 4.3% reduction in car accidents and 12.8% reduction in ED visits for CGM users within that time. This compares to a 4% increase in ED visits, 2.6% reduction in car accidents and 0% difference in hospitalization for non-CGM users within that same time period. The authors report unadjusted and adjusted odds ratios (and some p-values), but no confidence intervals, so it is not possible to properly comment on the statistical significance of the results.

Argento et al's study was a retrospective electronic health record review where the investigators looked at medically recorded hypoglycemia (requiring assistance from a third party). Here, CGM users were shown to have a reduction in severe hypoglycemic episodes from 52 (recorded in the five years before CGM initiation) to 12 after starting CGM. Overall, the proportion of patients with any severe hypoglycemia fell from 79% to 31% after initiation of CGM (7). However, we are conscious of the major limitations of these studies which are non-randomized, unblinded, and without any specific treatment protocols involving glucose-lowering drugs.

#### 4 Discussion

In this systematic review of CGM, we have evaluated 9 studies with a total of 989 participants who had type 1 or type 2 diabetes. There was a diverse range of study designs, ranging from pilot studies, mixed method studies, database observational studies and one RCT.

Despite the variation in study populations and geographical locations, we found consistent evidence that CGM was able to detect hypoglycemic episodes in a sizeable proportion of older patients, many of which were asymptomatic. In particular, van Dijk et al's reported that 100% of the CGM recorded hypoglycemic episodes were asymptomatic, with some patients having nearly two hours per day in hypoglycemic range (13). Munshi et al also highlighted that 95% of the captured hypoglycemic episodes went unrecognized (9). Clinicians and patients would probably have been completely unaware of these prolonged asymptomatic episodes in the pre-CGM era, and this may represent a major unrecognized health burden in older people with diabetes.

Linked to the asymptomatic hypoglycemic episodes, one could hypothesize that older patients (who may have cognitive problems and poor hypoglycemic awareness) are spending longer in the hypoglycemic range compared to patients with good hypoglycemic awareness, who are able to correct their blood sugar levels in a short amount of time. Whilst this appears to be a plausible theory, we are not able to substantiate this with evidence, as the included studies do not provide enough information on hypoglycemia awareness. Nevertheless, an important area for further research is whether an increased

risk of serious harm is associated with duration of time in hypoglycemic range rather than discrete episodes of hypoglycemic events.

In addition to picking up hypoglycemic events, the included studies have highlighted that older people with diabetes find the use of CGM acceptable (12) and that it improved well-being (8). Litchman et al also reported barriers regarding lack of accessibility, affordability and lack of insurance cover which can prevent older people from being able to make use of CGM technology (8). Although many of the studies do not directly draw a link between hypoglycemia and subsequent serious events that affect quality of life, we have found three studies that venture the possibility of an association with emergency department visits and ventricular arrhythmias (8) (10, 11).

Moreover, other meta-analyses have demonstrated significant associations between hypoglycemia and subsequent serious complications. One meta-analysis revealed that patients with impaired cognition had significantly greater likelihood of hypoglycemia (pooled odds ratio (OR) 1.61 (95% Confidence Interval (CI) 1.25, 2.06)) compared to those without. In turn, those affected by hypoglycemia were more susceptible to worsening cognitive impairment and dementia (OR 1.68; 95% CI 1.45, 1.95) (17). A further systematic review in older patients found a significant association between hypoglycemia and falls (OR 1.89; 95% CI 1.54, 2.32), or fractures (OR 1.92 95% CI 1.56, 2.38), and a near doubling of cardiovascular complications and death (18).

In addition to picking up hypoglycemic events, the included studies have highlighted that older people with diabetes find the use of CGM acceptable (12) and that it improved well-being (8). Litchman et al also reported barriers regarding lack of accessibility, affordability and lack of insurance cover which can prevent older people from being able to make use of CGM technology (8). The advent of flash glucose monitoring may be a more cost-effective way to optimize diabetes management.

We recognize important limitations of our systematic review. The data provided by the included studies was too heterogenous to provide an appropriate meta-analysis. We have therefore not been able to provide a quantitative analysis of the data. The included studies

range to mixed-method online surveys to RCTs, which makes it difficult to provide a robust analysis of the quality of the data and we only included English-language articles. Some of the studies had a very select group of participants (Caucasian, highly educated and users of technological devices) and small sample sizes (<50). This limits the generalizability to the general older population with diabetes.

Rather than using CGM all-year round, we believe it would be more cost-effective to use CGM to 'troubleshoot' (for example, two weeks every six months) and identify patterns in glucose variability (especially asymptomatic hypoglycemia) in older patients. Intermittent finger-prick testing is not useful in this group, because the vast majority of hypoglycemic episodes seem to be asymptomatic, and the older patient or carer may not be alerted to the need to do the finger-prick test at that point in time. In addition, the duration of time spent in the hypoglycemic range could not be reliably assessed through intermittent finger-prick testing.

Further studies should explore possible associations between CGM recorded hypoglycemic episodes, duration of time in hypoglycemic range and cognitive and cardiovascular outcomes. This could involve large cohorts of older people with diabetes (especially type 2 diabetes), with the aim of correlating asymptomatic hypoglycemic episodes with subsequent serious adverse outcomes (for example patients could be asked to wear a 14-day ECG recorder, in order to capture possible arrhythmias occurring at the time of hypoglycaemic episodes). In addition, trials of new glucose lowering therapies in older patients with diabetes should include the routine use of CGM, so that harmful effects are not missed. At present, the inconsistent definition and capture of hypoglycemic episodes can lead to a misleadingly rosy picture of glucose lowering therapy in older people because the true extent of harm is difficult to analyze whilst the potential beneficial effects may be over-emphasized (19).

We believe that the monitoring strategy in older patients should focus on preventing imminent or acute harm, rather than long-term complications related to HbA1C which may only manifest in 10-20 years' time which may be beyond the lifespan of some patients.

**5 Conclusions**

CGM is an innovative technology that can detect otherwise unrecognized hypoglycemic events in older patients. CGM can provide more robust evidence to inform the careful balance of avoiding harm from hypoglycemia and long-term diabetes control in such patients.

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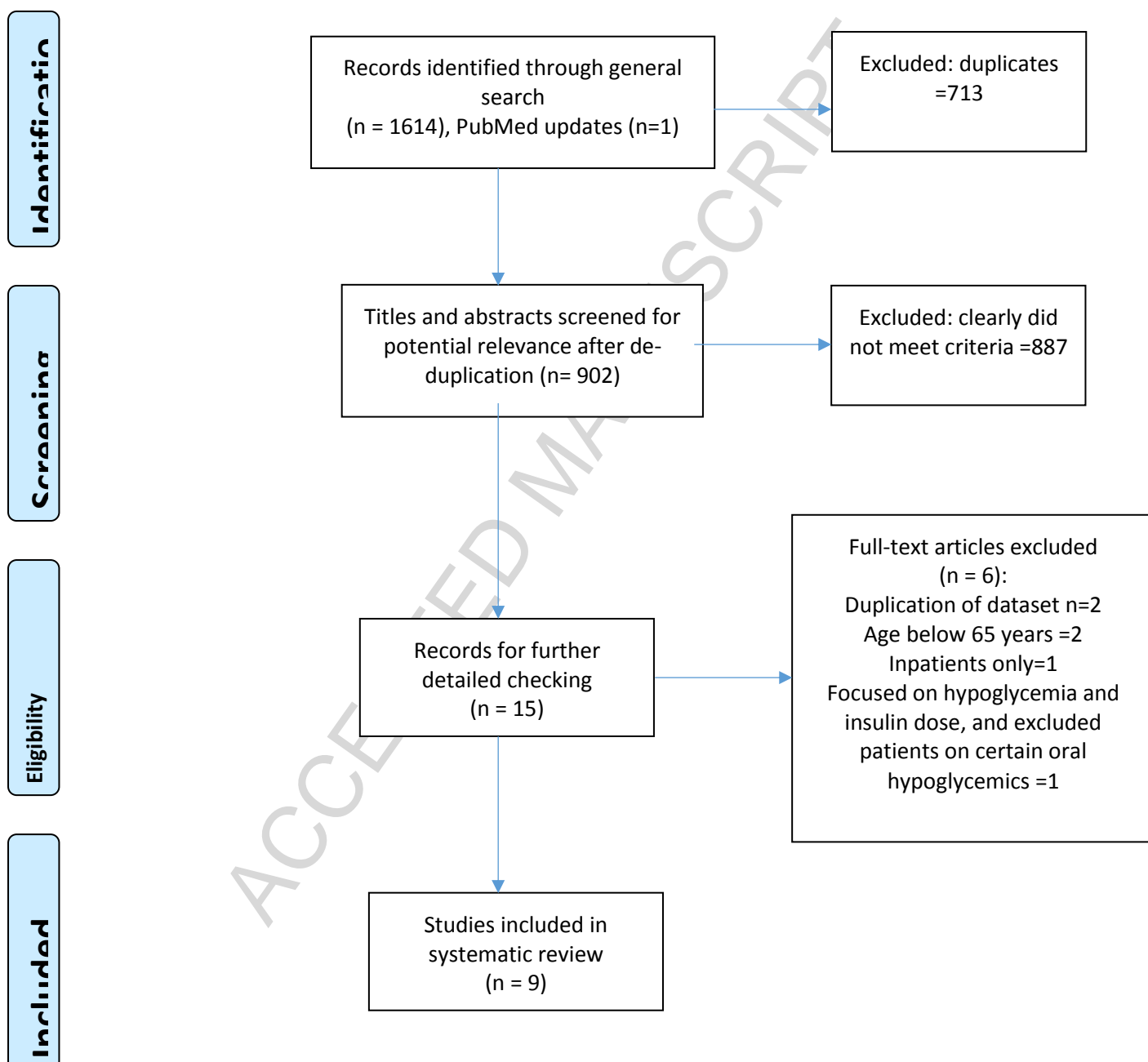
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Appendix A Figure A.1 PRISMA diagram of study selection



## PRISMA 2009 Flow Diagram



Appendix B Table B.1: Study design and characteristics

Study ID	Study design, setting, country	Patient Characteristics (numbers in each group, mean age overall, % male, type of diabetes, any inclusion/exclusion criteria, confounders adjusted for)	Intervention (which model/make of CGM), blinded or not
Argento 2014 (7)	Retrospective electronic health record review US adult endocrinology clinic. Any patient >65 years with CGM 15 June 2013	CGM (n=29) Age:68.8 (SD 3.5) years Male 12/29 (41%) T1DM 26/29 (90%) All patients used insulin	Device not stated No blinding
DuBose 2016 (15)	T1D Exchange Clinic Network in US.	Non-CGM users, T1DM >60 years age, diabetes duration >20years. Exclusions: chronic kidney disease stage 4 or 5, moderate or advanced dementia, or pancreatic transplant. N=199 Mean age 68 Male 53% Mean duration of diabetes 40 years	Blinded participants using Dexcom SEVEN device, sampling glucose every 5 minutes for a week. Device replaced after that for further 7 days.
Ishikawa 2017 (14)	Retrospective observational study previously collected CGM data, Chiba University Hospital and Kashiwado Hospital Japan 2011-2016.	N=170 (83% outpatients) type II DM age>65 years. Mean Age 74.1±6.7 42.4% on DPP-4 inhibitors, 55.9% on with insulin) and 27.1% on SU.	Medtronic iPro v2 or System Gold Blinded
Litchman 2017 (8)	Two online surveys of CGM through Diabetes Online Community on Facebook. Convenience sample using snowball sampling technique	N=11 users T1DM >65 years, able to read/write English. Mean age 69.6 ± 4 years Male: 55% Diabetes duration 59.4 ± 6.4 y Control group N=11 who want to use CGM	Dexcom Gen4 =8 Dexcom Gen 5 =1 Medtronic Revel=1 Medtronic Enlite =1  No blinding
Munshi 2011 (9)	Prospective observational study, Tertiary care diabetes clinic, USA.	N=40 Community-living patients aged ≥69 years with HbA1C>8%	Blinded Medtronic iPro sampling every 5 minutes for a 3-day period
Pistrosch 2015 (10)	Cross-sectional study of tertiary centre, Germany	N=94 Frail patients with type 2 diabetes with a proven cardiovascular event Mean age 68 years Males: Duration of diabetes:	Medtronic iPro2 sampling every 5 minutes for a 5-day period  Blinded
Polonsky 2016 (11)	Dexcom, Inc central database – email invites for participation in online survey in US	N=210 ≥ 65 years of age with Medicare as primary insurance or no health insurance coverage. Mean age 70.4 years M: 52.9%	Presumably Dexcom users  Unblinded

		Duration of diabetes 35.7 years T1DM: 93.8% T2DM: 6.2%	
Ruedy 2017 (12)	Multicentre RCT in US and Canada	N=63 on CGM, N =53 controls >60 years, receiving multiple daily insulin > 1 year, stable diabetes, compliant with Self-monitoring. Excluded if recent use of CGM. Mean age 67 years Duration of diabetes 21 years T1DM: 20 (32%) T2DM: 43 (68%)	Dexcom G4 Platinum  All participants had 2 weeks blinded CGM prior to allocation to intervention or control arms. Following that, intervention arm received unblinded CGM with algorithm for glucose control.
Van Dijk 2017 (13)	Primary care, Netherlands	N=23 Age $\geq$ 70 years, T2DM, HbA1c < 58 mmol/mol (7.5%), and a Groningen Frailty Indicator (GFI) score $\geq$ 4. Mean age 76 years Male 47% Median duration of diabetes 9 years	Blinded Medtronic iPro2

CGM= continuous glucose monitor, DM=Diabetes Mellitus, PCGM= personal real-time continuous glucose monitoring, RT-CGM=real-time continuous glucose monitoring, CKD=chronic kidney disease, T1DM=Type 1 Diabetes Mellitus, T2DM=Type 2 Diabetes Mellitus, SMBG=self-monitoring blood glucose, RCT= Randomised Controlled Trial, SH=severe hypoglycaemia, HE=hypoglycemic event, DKA=diabetic ketoacidosis, CVD=cardiovascular disease, AV block=atrioventricular block, PPM=permanent pacemaker, iG=interstitial glucose, QOL=quality of life, GFI=Groningen Frailty indicator, OR= Odds Ratio, 95%CI= 95% Confidence Interval, SU= sulfonylurea, DPP4 inhibitor=dipeptidyl peptidase-4 inhibitor, HbA1c=haemoglobin A1c, VT=ventricular tachycardia

Appendix B Table B.2: Outcomes

Study ID	Summary statistics of blood sugar values captured (mean, median, range, standard deviation) Recording time	Definition and number of hypoglycemic episodes captured	What types of adverse events of interest were specified or defined?	How and when were adverse events ascertained?	How complete was follow-up and reporting of adverse events? (duration, numbers for loss to follow-up, or selected sample only)	Was patient adherence and device acceptability ascertained?
Argento 2014 (7)	CGM duration 36.8 (range 4-68) months Pre- vs. post-CGM outcomes: Percent with hypo pre: 79% vs..31% (P = .0002, n = 29). No. of hypos: pre- 52 episodes in 5 years prior vs. 12 episodes after initiating PCGM. (5 SH episodes occurred while patients not using PCGM). Yearly rate of SH $0.37 \pm 0.38$ vs. $0.12 \pm 0.19$ (P = .0007)	Severe if patient required third-party assistance and counted as present if there was at least 1 recorded episode. Individual reports of SH were counted as single episodes, and if plural or many episodes, then classified as several	Not stated	Not stated	38 prescribed PCGM; 29 were still regularly using PCGM, 2 were using professional CGM intermittently, and 7 never started PCGM (3 patients) or discontinued  Intermittent users excluded	Not stated.
DuBose 2016 (15)	Median 286 hours out of potential maximum of 336 hours CGM in two weeks.	CGM recorded hypos; Minutes per 24 hrs (% time) <3.9 mmol: 91 (6.3%) <3.3 mmol: 55 (3.8%) <2.8 mmol: 31 (2.2%)  % days with at least one hypo event 38%	Not stated	Not stated	Missing data varied from 3 – 15 participants according to category of > 6 hours missing data per time period (24 h, day only, night only)  199/201 patients followed-up	Not stated
Ishikawa 2017 (14)	Glucose recordings: < 3.9 mmol: 72/170 % of time in hypo: 2.3%	< 3.9 mmol, no mention of clinical event	Not stated	Not stated	Not stated	Not stated
Litchman 2017 (8)	10/11 users said they had it on all the time.	Hypoglycemia glucose < 3.9 mmol;; severe	Hospitalization	Online survey	Selected sample – self-identified as high	Yes. why participants were using/wanted

		hypoglycemia hypoglycemia episode requiring assistance from another person, hypoglycemia unawareness is defined as occurring when an individual with diabetes is experiencing hypoglycemia, but feels no symptoms.			technology users	to use RT- CGM, and how RT-CGM was affecting/might affect diabetes management and safety
Munshi 2011 (9)	65% of patients with A1C >8% were found to have ≥1 hypoglycemic episode over a 3-day period.  4 times a day finger- stick glucose checks did not coincide with CGM- detected hypoglycemia	Symptoms – self- report. Analysis of CGM according to time, duration and magnitude of low glucose  65% (26/40 patients) ≥1 hypoglycemia (median glucose 63 (42–69) mg/dl). 12 (46%) had glucose levels <50 mg/dl, and 19 (73%) <60 mg/dl. Average number of episodes 4 with average duration of 46 minutes. Of a total of 102 hypoglycemic episodes, 95 (93%) were unrecognized, either by finger- stick monitoring or by symptoms. 18/ 26 (69%) had ≥1 nocturnal episode (average duration 56 minutes).	Not stated	Not stated	Not stated	Not stated
Pistrosch 2015 (10)	Patients perceived only 39 % of HE during the day and 11 % of HE during the night. Patients with HE	<3.1mmol 26/94 patients had hypo. Fifty-four episodes of	Cardio vascular events (VT)	24-hour ECG monitoring	Not stated	Not stated

	<p>had significantly higher number of severe ventricular arrhythmias [ventricular tachycardia (VT) <math>32.8 \pm 60</math> vs. <math>0.9 \pm 4.2</math>, <math>p = 0.019</math>], and multivariate regression analysis revealed the duration of severe HE and TSH level as independent predictors of the occurrence of a VT</p>	<p>hypoglycemia (average of 2.4 episodes per patient), with 171 minutes mean duration over 5 days. Eighteen events during daytime and 36 nocturnal <math>&lt;3.9</math> mmol/L episodes per patient with 415 minutes mean duration over 5 days.</p> <p>Patients asked to record all symptoms of hypoglycemia with date and time in diary</p>				
Polonsky 2016 (11)	<p>154 (73.3%) in 6 months prior to CGM as compared to recent 6 months with CGM 121 (57.6%). Drops in the incidence of events requiring the assistance of another, hypoglycemia-related hospitalizations, ER visits, paramedic visits to the home, and auto accidents</p>	<p>Hypoglycemia frequency of low blood glucoses (<math>&lt;70</math> mg/dl) in the past month, with and without symptoms; over the past 6 months, the frequency of moderate hypoglycemic episodes (symptoms of confusion, disorientation, lethargy or being unable to treat oneself) and the number of a variety of events associated with severe hypoglycemia, including episodes requiring assistance. Comparison of frequency/number of events during the "retrospective</p>	<p>Health care use including paramedic visit, emergency department care, road accidents.</p>	<p>Online survey</p>	<p>Online survey conducted on behalf of Dexcom (CGM manufacturer)</p>	<p>Not stated</p>



		baseline period," defined as the 6-month period before they first started RT-CGM vs. current period.				
Ruedy 2017 (12)	Mean CGM use was 6.9 ± 0.2 days/week in month one; and 6.8 ± 1.1 in month 6.  HbA1c reduction from baseline to 24 weeks was greater in the CGM group than Control group (-0.9 ± 0.7% versus -0.5 ± 0.7%, adjusted difference in mean change -0.4 ± 0.1%, P < .001).	Severe hypoglycemia (SH) event that required assistance from another person to administer carbohydrates or other resuscitative action No serious hypos recorded during study. CGM recorded hypos at baseline: Median minutes per 24 hrs (% time) at <3.3 mmol was 10 (0.7%) for intervention arm and 8 (0.6%) for control arm.	Not stated	Not stated	Post-hoc analysis of multicentre RCT	Satisfaction with use of CGM mean score of 4.2 ± 0.4 on the CGM Satisfaction Survey (possible score range 1 to 5), with mean scores of 4.3 ± 0.5 on the Benefits subscale and 1.8 ± 0.5 on the Hassles subscale
Van Dijk 2017 (13)	Monitoring period – 97 hours median (out of maximum of 120 hours)	Hypo < 3.0mmol: 5 patients had 15 events (245 minutes total) Hypo <3.5 mmol: 8 patients had 25 events (292 minutes total). None of the patients reported symptoms.	Not stated	Not stated	Not stated	Not stated

CGM= continuous glucose monitor, DM=Diabetes Mellitus, PCGM= personal real-time continuous glucose monitoring, RT-CGM=real-time continuous glucose monitoring, CKD=chronic kidney disease, T1DM=Type 1 Diabetes Mellitus, T2DM=Type 2 Diabetes Mellitus, SMBG=self-monitoring blood glucose, RCT= Randomised Controlled Trial, SH=severe hypoglycaemia, HE=hypoglycemic event, DKA=diabetic ketoacidosis, CVD=cardiovascular disease, AV block=atrioventricular block, PPM=permanent pacemaker, iG=interstitial glucose, QOL=quality of life, GFI=Groeningen Frailty indicator, OR= Odds Ratio, 95%CI= 95% Confidence Interval, SU= sulfonylurea, DPP4 inhibitor=dipeptidyl peptidase-4 inhibitor, HbA1c=haemoglobin A1c, VT=ventricular tachycardia