Point-of-care HbA1c tests - diagnosis of diabetes

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Clinical Question:

In a primary care setting, what is the utility of HbA1c point-of-care testing (POCT) devices in the detection/diagnosis of diabetes mellitus (DM), compared to standard laboratory methods for HbA1c analysis?

Background:

Diabetes mellitus (DM) is a chronic metabolic disorder primarily characterised by a defect in insulin secretion, action or both, leading to permanent hyperglycaemia. The most common types include type 1 and type 2 DM.

DM represents a major health problem of the 21st century, causing severe long-term damage to the cardiovascular and nervous system as well as eyes and kidneys. The World Health Organization (WHO) estimated 1.5 million deaths in 2012 to be directly caused by diabetes (1).

Most cases (90%) of DM are type 2, which arises from defects in insulin action leading to insulin resistance, often combined with defects in insulin secretion. Circulatory insulin levels therefore may be normal or raised, but it cannot be used effectively. This subtype is predominant in middle-aged overweight patients with a sedentary lifestyle. In 2011 the WHO advocated the use of HbA1c for the diagnosis of type 2 DM and in 2012 UK guidance followed suit (2, 3).

Haemoglobin A_{1c}

The concentration of glycated haemoglobin (HbA_{1c}) is a surrogate measure for the average circulating glucose level over the previous 120 days (typical lifespan of a red blood cell) as well as a strong marker of complications associated with diabetes. It is therefore used as a clinical tool for monitoring of glycaemic control in people with diabetes (4).

Haemoglobin A_{1c} is formed by glycation of the N-terminal valine of the beta chain of haemoglobin, which is a non-enzymatic reaction occurring within red blood cells and resulting in an increased negative charge of the molecule. The more glucose is present in the blood stream during the lifetime of the red blood cells, the higher the concentration of HbA_{1c}.

Current practice and advantages over existing technology:

The clinical process to assess patients with suspected diabetes typically involves at least two appointments with a GP/practice nurse; blood samples being taken during the first visit and 1-2 weeks later results being discussed with the patient, after laboratory analysis. If an elevated HbA1c is found and there are no other symptoms then a repeat blood test would normally be undertaken, adding to the length of time taken to reach a diagnosis. Furthermore, once diagnosed with diabetes, HbA_{1c} concentration is monitored on a regular basis (every 3-6 months) to assess control of blood glucose concentration (5).

As an alternative, point-of-care testing (POCT) aims to provide immediate results at the time of patient consultation to enable therapeutic decisions to be made at the earliest possible opportunity, resulting in fewer patient visits and improved glycaemic control. POCT is defined as clinical testing close to the site of patient care, typically with small/portable instruments.

There is some evidence supporting the use of POCT for HbA_{1c} analysis: studies report on an overall improvement of clinical outcomes in the primary as well as secondary care settings after usage of POCT in the management of diabetes (6).

Details of Technology:

Most POCT devices for HbA_{1c} use a drop of capillary whole blood, collected via the finger-prick procedure. Following application to the test cartridge, the sample is analysed within a few minutes using methods based on either differences in structure or charge of the glycated vs non-glycated haemoglobin.

Cation-exchange chromatography: Haemoglobin species (HbA_{1c} and HbA_0) are separated based on the difference in isoelectric point, by employing differences in ionic interactions between the haemoglobin in the blood sample and the cation exchange groups on the column resin surface.

Immunoassay: The immunoassay method uses antibodies which bind to the N-terminal glycated tetrapeptide or hexapeptide group of the HbA_{1c}, forming immunocomplexes which can be detected and measured using a turbidimeter or a nephelometer.

Affinity chromatography: Affinity chromatography is a separation technique based on structural differences between glycated vs non-glycated haemoglobin which utilises m-aminophenylboronic acid and its specific interactions with the glucose adduct of glycated haemoglobin.

Enzymatic assay: Enzymatic quantification of HbA_{1c} is based on cleavage of the beta chain of haemoglobin by specific proteases to liberate peptides, which then further react to produce a measurable signal (4).

Table 1: Table of key characteristics of available POCT device for HbA_{1c} – manufacturers claims.

Product	Manufacturer	Blood type analysed	sample volume (µL)	Analysis time (mins)	Weight (kg)	Dimensions	Detection Range/ Limit	Method Principle	Im-precision (%CV)	NGSP certified	FDA approved	CLIA waived
Afinion AS100 Analyzer	Alere Technologies AS, Norway	c/v	1.5	3	5.0	320 mm x 170 mm x 170 mm	20.2-140.4mmol/mol (4.0-15.0%)	Boronate affinity	<3%	Yes	Yes	Yes
ERA-STAT 2000	Ceragem Medisys Inc, South Korea	c/v	5	<3	0.73	178 mm x 195 mm x 75 mm	9.0-140.4mmol/mol (3.0-15.0%)	Boronate affinity	no info	Yes	Yes	No
Clover	Infopia, Korea	c	4	5	1.5	200 mm x 200 mm x 139 mm	20.2-129.5mmol/mol (4.0-14.0%)	Boronate affinity	<1%	Yes	No	No
HemoCue Hba1c 501 System	Infopia/ Hemocue, Sweden	c	4	5	1.6	198 mm × 217 mm × 136 mm	20.2-129.5mmol/mol (4.0-14.0%)	Boronate affinity	<3%	Yes	Yes	Yes
Huma Meter A1c	HUMAN Diagnostics Worldwide, Germany	c/v	4	4	0.7	200 mm x 85 mm x 130 mm	20.2-140.4mmol/mol (4.0-15.0%)	Boronate affinity	<3%	Yes	No	No
Labona-Check A1c	Ceragem Medisys Inc, South Korea	c/v	5	<3	0.73	178 mm x 195 mm x 75 mm	9.0-140.4mmol/mol (3.0-15.0%)	Boronate affinity	2.8-3.8%	Yes	Yes	No
Nycocard	Alere Technologies AS, Norway	c/v	5	3	0.54	200 mm x 170 mm x 70 mm	20.2-140.4mmol/mol (4.0-15.0%)	Boronate affinity	<3%	Yes	No	No
Quo-Lab HbA1c Analyser	Quotient Diagnostics, UK	c/v	4	4	0.7	205 mm x 135 mm x 95 mm	20.2-140.4mmol/mol (4.0-15.0%)	Boronate affinity	<3%	Yes	No	No
Quo-Test	Quotient Diagnostics, UK	c/v	4	4	1.3	205 mm x 135 mm x 205 mm	20.2-140.4mmol/mol (4.0-15.0%)	Boronate affinity	<3%	Yes	No	No

Tri-Stat HGB A1C	Trinity Biotech Plc, Ireland	c	3.5	10	3.0	255mm x 275 mm x 115mm	20.2-129.5mmol/mol (4.0-14.0%)	Boronate affinity (Fluorescence Quenching)	<3%	Yes	Yes	No
A1c iGear	Sakae Corporation, Tokyo	c/v	1	6	No info	230 mm x 280 mm x 290 mm	20.2-119.0mmol/mol (4.0-13.0%)	Immuno-assay	<3%	Yes	Yes	No
A1cNow+	PTS/Chek Diagnostics, USA	c/v	5	5	0.18	51 mm x 63.5 mm x 10 mm	20.2-119.0mmol/mol (4.0-13.0%)	Immuno-assay	3.0-4.02%	Yes	Yes	Yes
B-Analyst	Menarini Diagnostics, UK	c/v	4	7.7	9.5	340 mm x 290 mm x 270 mm	13.0-114.0mmol/mol (3.3 -12.6%)	Immuno-assay	0.8%	Yes	No	Yes
i-CHROMA	Boditech Med Incorporated, Korea	c	5	10	1.2	185 mm x 250 mm x 80 mm	20.2-140.4mmol/mol (4.0-15.0%)	Immuno-assay	<5%	Yes	No	No
Cobas b 101 POC system	Roche Diagnostics Limited, Switzerland	c	≤2	≤5.7	2.0	184 mm x 135 mm x 234 mm	20.2-129.5mmol/mol (4.0-14.0%)	Immuno-assay	<4%	Yes	Yes	No
Cube	Eurolyser Diagnostica GmbH, Austria	c	10	7.5	2.4	160 mm x 130 mm x 145 mm	20.2-129.5mmol/mol (4.0-14.0%)	Immuno-assay	<1.2%	No	No	No
DCA 2000+	Bayer Diagnostics Europe, Ireland	c/v	1	6	5.0	239 mm x 241 mm x 272 mm	3.8-129.5mmol/mol (2.5-14.0%)	Immuno-assay	2.6%	Yes	Yes	Yes
DCA Vantage	Siemens Medical Diagnostics, New York	c/v	1	6	3.9	287 mm x 277 mm x 254 mm	3.8-129.5mmol/mol (2.5-14.0%)	Immuno-assay	<3%	Yes	Yes	Yes
InnovaStar	DiaSys, Germany	c/v	10	6.5	4.0	200 mm x 170 mm x 150 mm	9.0-130.0mmol/mol (3.0-14.0%)	Immuno-assay	<2%	Yes	No	No

SD A1c Care	SD Biosensor, Korea	c/v	5	3	0.45	163 mm x 96 mm x 56 mm	20.2-140.4mmol/mol (4.0-15.0%)	Immuno-assay	≤3%	Yes	No	No
Skyla A1c	Liteon Technology corporation, Taiwan	c	1	5	1.7	271 mm x 188 mm x 148 mm	20.2-129.5mmol/mol (4.0-14.0%)	Immuno-assay	no info	No	No	No
Smart 700/340	Eurolyser Diagnostica GmbH, Austria	c	10	7.5	3.4	260 mm x 145 mm x 140 mm	20.2-129.5mmol/mol (4.0-14.0%)	Immuno-assay	< 1.2 %	Yes	Yes	no info
DS5	Drew Scientific Group, USA	c	20	5	20.0	270 mm x 410 mm x 350 mm	20.2-173.0mmol/mol (4.0-18.0%)	Cation exchange chroma-tography	no info	Yes	Yes	No
Glycohemoglobin Analyzer RC20 (ラピッドカラム® A1c)	Sekisui Medical, Tokyo	c	3	3	11.2	190 mm x 380 mm x 360 mm	20.2-140.4mmol/mol (4.0-15.0%)	Cation exchange chroma-tography	low: 0.61% mid: 0.39% high:0.28 %	No	No	No

Note: there are no bias claims from manufacturers as these should all be calibrated to the IFCC reference measurement procedure

Patient Group and Use:

It is likely that HbA_{1c} POCT devices are used in some clinical care settings to diagnose type 2 diabetes, although no specific guidelines support the utilisation of POCT of glycated haemoglobin for diagnostic purposes at present.

The WHO guidance states that HbA1c may be used for diagnosis of type 2 DM provided "stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values"(3). For laboratory based methods the quality standards for HbA1c as a diagnostic tool and HbA1c as a monitoring tool are the same. Quality targets vary, depending on the organisation or body giving the guidance; however the IFCC recently proposed the use of sigma metrics to define and set quality targets that can be adjusted depending on the specific requirements of the system/setting being assessed(7). Currently there is no further additional guidance that specifically relates to quality targets for POC devices for HbA1c.

Importance:

In 2014, the WHO estimated the global prevalence of DM to be 9% amongst adults over 18 years and predicted it to be the 7th most common cause of death by 2030 [1]. Approximately 90% of all cases of diabetes are type 2 DM. Whilst 45.8% of all cases of DM amongst adults are estimated to be undiagnosed, the detection of the condition and adequate glycaemic control is crucial to managing the course of the disease as treatment and therapies need to be adjusted in order to minimise micro- and macrovascular complications including nephropathy, neuropathy and retinopathy (8).

Previous Research:

Accuracy compared to existing technology

A strategic literature search was performed on Medline, Embase, Scopus, CINAHL, Cochrane library, Trip and Web of Science. The MeSH terms used were "Hemoglobin A, Glycosylated" AND "Point-Of-Care Systems" and a supplementary search was conducted for the terms HbA_{1c} or synonyms combined with POCT or interchangeable terms, as well as for known brand names of POCT devices.

The following section brings into focus a brief overview of the POCT devices currently available for HbA_{1c} analysis. Data presented represent the full range of reported findings across all studies. Meta-analysis of the findings was not performed. Please also refer to Tables 1 and 2 for further, detailed information.

A1cNow+ (PTS/Chek diagnostics)

The A1cNow+ analyser is currently the smallest portable device, using capillary or venous blood. The principle for analysis of HbA_{1c} is based on an immunoassay. Two laboratory based studies, with 55 and 54 included patient samples respectively, have investigated the precision of the device and

reported a coefficient of variation (CV) ranging from 2.74% at a low (31 mmolmol (5%)) HbA_{1c} to 4.02% at a high (75mmol/mol (9%)) HbA_{1c} concentration (9, 10). Regarding accuracy, six studies, with a minimum of 47 and a maximum of 1618 patient samples, reported a wide overall bias range of -12.0 to +21.9 mmol/mol (-1.1% to +2%) (9-14). Only one of these studies was conducted in a laboratory setting with laboratory trained staff (9), the remaining studies were conducted by non-laboratory professionals. The A1cNow+ analyser is easy to use (10, 13, 14) and can be operated anywhere due to its light weight. The device is Clinical Laboratory Improvement Amendments (CLIA) waived in the United States, and therefore is approved for use by an untrained person provided clear instructions are given.

Cobas b 101 (Roche Diagnostics Limited)

Based on the same methodological principle, the Cobas b 101 analyser is able to detect an HbA_{1c} concentration between 20-130mmol/mol (4.0-14.0%) within less than six minutes. According to three recent evaluations, coefficients of variation ranged from 1.2% to 2.8% (assumed total CV) (15-17). In two of the three studies, HbA_{1c} analysis was performed in a laboratory setting by laboratory trained staff with 79 and 40 patient samples, respectively. The remaining study included 41 patient samples but the operator was not specified. The reported mean bias covers values between -0.9 to +1.1 mmol/mol (-0.08% to +0.10%) (15, 16). One study found further that at HbA_{1c} values of more than 86 mmol/mol (10%), the instrument showed a strong proportional negative bias (17). This indicates that the bias is not even across the range of values and may be indicative of a standardisation or calibration issue.

It is recommended not to use the Cobas b101 analyser in regions where the prevalence of Hb AE variants is high, due to possible interference (16).

A1c Gear (Sakae Corporation)

The A1c Gear HbA_{1c} analyser uses an immunoassay method (immuno-turbidimetric) and only requires a small sample of capillary or venous blood to deliver results within six minutes. A single study, utilising 120 patient samples, compares the performance of this device with the Bio-Rad Variant™II (laboratory analyser) in the hands of laboratory trained staff, in a laboratory setting. A small negative bias of -2.7 mmol/mol (-0.25%) for HbA_{1c} concentrations <102 mmol/mol (<11.5%) and a total imprecision of 1.67-2.35% was reported, which is within the range claimed by the manufacturer. The presence of the S haemoglobin trait in some of the analysed samples did not appear to negatively impact the measurements (18).

DCA 2000(+) and DCA Vantage (Siemens Medical Diagnostics)

The DCA 2000(+) is a discontinued product which has been upgraded by the manufacturer to the DCA Vantage, the latter of which has a better interface but uses the same reagents and basic methodology (immunoassay) as the older model. However, there are still a large number of DCA 2000(+) analysers in use and therefore information on the instrument is still relevant.

In a study using 80 samples from people with diabetes, the DCA 2000 showed a total CV of 3.4% at a low HbA_{1c}, and at a higher level a CV of 7.3% (19). A mean bias of a difference of 5% from target value was also reported with a range from -27.6 to 15.8%. The detection range of the analyser covers 27-130 mmol/mol (2.5-14.0%), testing either capillary or venous blood.

Eight recent studies have evaluated the performance of the DCA Vantage, which is a lighter instrument (3.9 vs 5.0 kg). Five of the trials were performed in a laboratory setting with 40 (16, 20, 21), 53 (22) and 100 patient samples (23), respectively; the remaining three studies had a sample size of 40 (24), 50 (25) and 88 (26), but did not state the study setting. The reported bias of all eight trials ranges from -5.0 to +3.5 mmol/mol (-0.46% to +0.32%) (16, 20-26) and imprecision analysis, included in six of the identified studies, showed better overall results than for the DCA 2000+ with a range of 0.7-5.5% (16, 20-23, 26). Lenters- Westra *et al*, described that performance of the analyser was lot number-dependent (20) in one study. In another study Szymezak, *et al*, described the instrument as having good ergonomics and user-friendliness (23).

InnovaStar (DiaSys)

The InnovaStar HbA_{1c} instrument measures the concentration of HbA_{1c} within 6.5 minutes, using the turbidimetric immunoassay method. The test procedure requires users with laboratory experience and as such may limit its role as a point of care device (27). Two studies focused on the performance of the device, both of them had a sample size of 40 and HbA_{1c} analysis was performed in a laboratory setting. Bias was found to range from -5.1 to -1.7 mmol/mol (-0.47% to -0.16%) (16, 21). Furthermore, one study found that their quality goal for accuracy was not fulfilled, requiring ≥95% of results to not deviate from the results of the comparison method by ≥ ±10% (27).

B-Analyst (Menarini Diagnostics)

The B-Analyst immunoassay device has greater dimensions and is heavier than the previously listed analysers. A recent laboratory based trial of 40 samples found imprecision results to range from 0.46-3.0% (assumed total CV). The B-Analyst has been considered to be suitable for diagnostic purposes, by the author of the study (16). A small positive bias was reported for the instrument, in agreement with a second study (120 samples, laboratory based study), ranging from +1.1 to +2.1 mmol/mol (+0.11% to +0.19%) (16, 28).

SD A1c Care (SD Biosensor)

The lightweight POCT device manufactured by SD Biosensor has a short analysis time of three minutes using an immunoassay-based procedure. Limited evidence exists on the performance of the analyser, given that only one study has assessed the performance of the device so far. The trial included the analysis of 150 patient samples by laboratory trained professionals in a laboratory setting; results showed a precision of 2.6-4.5% CV and a very small positive bias of +0.4 mmol/mol (+0.04%) (29).

Afinion AS100 (Alere Technologies)

The Afinion AS100 is a small benchtop analyser using boronate affinity chromatography for separation of glycated vs non-glycated haemoglobin. Investigation of imprecision in seven individual studies mostly run by laboratory trained staff (using a range of 40-135 patient samples), produced a mixed range of results from 0.7-2.5% for between-day, 0.5-2.2% for intraday and 0.9-2.7% for total CV (16, 21, 22, 26, 30-32). Regarding accuracy, the range of the total bias is -4.5 to +3.1 mmol/mol (-0.41% to +0.28%). Interestingly, there have been contradictory conclusions from different studies regarding the use of the analyser: one evaluation investigating the conformance of several POCT devices suggests that the Afinion AS100 may be suitable for diagnosis of DM, whereas other sources

recommend not to use the instrument for this purpose, given the wide reported bias range (22, 33). However, these recommendations are based on polices local to the authors, at present there is insufficient evidence to make a recommendation for use in the diagnosis of diabetes.

Nycocard (Alere Technologies)

The Nycocard analyser is marketed by the same manufacturer as the Afinion and uses the same analytical methodology. Overall, studies in both laboratory and clinical settings and including data from a national EQA scheme, report on a poor performance of the device (21, 34, 35), giving duplicate patient sample CVs of 15.9%, within-batch CV of 5.6-6.9% and between-batch CV of 5.8-13.1% (21, 25, 35). A nurse-based evaluation comparing performance of the analyser when handled by laboratory trained vs non-laboratory trained professionals reports on frustration felt by the staff due to several manual steps and the need of constant attention, as well as several error messages which lead to erroneous data (35).

Quo-Test (Quotient Diagnostics)

The fully automated Quo-Test device is able to analyse a sample of 4µl within 4 minutes, using boronate affinity chromatography for separation of glycated vs non-glycated haemoglobin. According to two similar, laboratory based, studies with a sample size of 40 each, the total CV yielded by the POCT method ranges from 1.6% at a high HbA_{1c} concentration to 5.9% at a low level (16, 36). Accuracy was found to range from -6.8 to +4.4 mmol/mol (-0.62% to +0.4%) (16, 33), and data from an additional trial which found significant differences between lot numbers (36).

Quo-Lab HbA_{1c} analyser (Quotient Diagnostics)

The Quo-Lab analyser is only semi-automated but lighter than the Quo-Test device and requires the same sample volume and analysis time as the Quo-Test and is likewise based on the biochemical procedure of boronate affinity separation. One study identified that the total CV reported is smaller than for the Quo-Test analyser, with a range from 1.7% at a high level to 3.1% at a low HbA_{1c} concentration. In this laboratory based trial of 40 patient samples the device showed an overall negative bias (SI -6.6 to -2.6 mmol/mol; -0.6 to -0.24%), (16).

Clover (Infopia)

The Clover HbA_{1c} is a portable device, which uses the same methodological principle as the Quo-Lab analyser. There is only one study which investigated the performance of the analyser using 40 patient samples, in the hands of laboratory trained staff, reporting on a high total CV of 3.5-4.0% and a negative bias ranging from -10.8 to -0.4 mmol/mol (-0.99 to -0.04%). An unacceptable lot number dependency was observed (21), with a high variation in values dependant on the lot number used, and the total imprecision was also too high for optimal clinical use, according to the authors' local policy.

Other instruments

In addition, the following POCT analysers for HbA_{1c} analysis are currently available on the market: Cera-Stat 2000, HemoCue HbA1c 501, HumaMeter A_{1c}, Labona-Check, Tri-Stat HGB A_{1c}, Cube, i-

Chroma, Skyla A_{1c}, Smart 700/340, DS5 and Glycohemoglobin Analyzer RC20 (table 1); however, no studies addressing the utility of these devices were found.

Impact compared to existing technology

Most POC testing devices have been found to be easy to learn and use by the intended users however some analysers such as the Innovastar and the Nycocard are more complicated to operate than other due to impacting factors such as long sample preparation times (Nycocard) and larger dimensions such as the B-analyst. The DCA family of analysers, the A1c Now and the Affinion analyser are the most commonly investigated analysers and on the whole there were positive reports for each in terms of usability. There were some conflicting reports for the A1c Now device which was described in one study as simple to operate by non-laboratory staff but in another, was not recommended for use outside of the laboratory, however this more relates to the analytical performance of the device in that study rather than how user-friendly the device was. For further detail refer to Table 2.

Health Economics:

A recent study in Ontario evaluates the cost difference between point-of-care and laboratory testing of HbA_{1c}, using the A1cNow+, DCA Vantage and In2it analysers (discontinued product). Results showed, that the annual costs for 2013/14 of POCT vs laboratory HbA_{1c} testing were $86.8 million vs $91.5 million, meaning that a replacement of all laboratory measurements by POCT would possibly save $4.7 million over the next year (37). A second study came to the conclusion that the total cost of HbA_{1c}determination by a POCT analyser (DCA) vs D10 (standard laboratory HbA_{1c} analyser) is lower (38), which again indicates that the introduction of more HbA_{1c} POCT is economical. Both of these studies relate to the use of HbA1c for the monitoring of people with diabetes, to date no studies have looked at this with respect to diagnosis of type 2 DM and as such there is a need for further health economic studies.

Table 2: Key findings of evaluations of POCT devices for HbA1c

Product	Imprecision	Ref.	Bias SI mmol/mol (NGSP %)	Ref.	Comments
Afinion (AS100)	Total CV ranges from 0.9-2.7%; intraday precision: 0.5-2.2%; between-day precision: 1.00-2.5% (low level) and 0.5-0.72% (high level)	(16, 21, 22, 26, 30-32)	Ranges from -4.5 to +3.1 mmol/mol (at HbA1c 5%)(-0.405% to +0.28%)	(16, 21, 22, 26, 30, 33, 39)	Demonstrated a calibration problem (21); operators found the Afinion AS100 Analyzer easy to learn and use (30); Lot-to-lot variation for the methods is a concern (32); Afinion instruments were also below the recommended limit of 3% for within-method between-laboratory variations in the majority of the surveys (34); repeatability and method/device precisions of D-10 and Afinion were acceptable; analyser can be used interchangeably with D-10 (Bio-Rad, USA), Variant II Turbo (Turbo; Bio-Rad, USA) and Cobas Integra 800 (Integra; Roche, Switzerland) (31); not to be used for the diagnostic purposes (22, 33). Operators experienced the device to be easy to use and identified, in comparison with the DCA 2000+, faster analysis time and easier sample loading as a considerable advantage of the Afinion (30).
Clover	At HbA1c 5.0% and 11.9%: total CV 4.0% and 3.5%	(21)	Ranges from -10.5 to -0.04 mmol/mol (-0.985% to-0.037%)	(21)	Lot number dependency of the Clover was unacceptable (21)

Nycocard	Total CV range 3.62-5.3% at lower level and 1.85-5.2% at higher level; within batch imprecision: 5.6-6.9% and between batch 5.8-13.1%; duplicate patient samples CV 15.9%	(21, 25, 35)	Ranges from -3.4 (at HbA1c 6.5%) to +7.3 mmol/mol (-0.3146% to + 0.67%)	(21, 25, 34, 35)	Frustration felt by the nursing staff when using the device: several manual steps and constant attention, a requirement that can be problematic in a busy clinic environment while it gave a relatively large number of error messages and no usable data as a result poor performance; Laboratory staff achieved a better performance than the nurses with the NycoCard method (35); did not meet the acceptance criteria of having a total CV <3% in the clinically relevant range; showed the worst imprecision of all the systems tested (21); Nycocard instrument did not meet the 3% recommendation for within-method between-laboratory variations in any of the surveys (34)
Quo-Lab	CV ranges from 1.7% (high level) to 3.1% (low level) (assumed total CV)	(16, 17)	Ranges from -6.6 to -2.6 mmol/mol (-0.6% to -0.24%)	(16, 17)	Needs to be calibrated and certified with fresh patient samples instead of frozen material (16); POC Negative bias could contribute to significant differences in therapeutic options and alter patient outcomes (17)
Quo-Test	Total CV: 5.9% (low level); 1.9-4.5% (medium level); 1.6-2.9% (high level)	(16, 36)	Ranges from -6.8 to +4.4 mmol/mol (at HbA1c 5%) (-0.62% to +0.4%)	(16, 33, 36)	Manufacturer decided not to continue the evaluation because of disappointing EP-10 results, however Quo-Test was a prelaunch instrument and was still in development (21); not to be used for the diagnostic purposes (33); needs to be calibrated and certified with fresh patient samples instead of frozen material (16); significant differences between lot numbers; according to authors, study proves that an NGSP certification does not guarantee the quality of results produced in the field and confirms the recommendation of the American Diabetes Association not to use Hb A1c point-of-care assays for diagnostic purposes at this time (36).

A1c iGear	Within-run imprecision: 0.87–1.33%; between-run imprecision: 1.41–2.35% ; total imprecision of 1.67–2.35%	(18)	Small negative bias (−0.25% HbA1c) for sample HbA1c concentrations < 11.5%	(18)	Presence of the S haemoglobin trait in a few of the samples evaluated did not negatively impact HbA1c measurements; excellent within day and between day precision (18).
A1cNow (Assumed withdrawn but may still be in circulation)	Total CV range 2.71 (at HbA1c 9.2%)- 6.8% (at Hba1c 6%); within batch imprecision: 3.0-8.7% and between batch ranges from 6.6-8.4%	(32, 35, 40-42)	Ranges from -1.6 (at HbA1c 6.5%) to +10.4 mmol/mol (-0.15 to + 0.95%)	(35, 40-46)	Not recommended for measurement of HbA1c outside of the laboratory (35); in one study, manufacturer decided not to continue the evaluation because of disappointing EP-10 results - bias found with the EP-10 protocol of the A1CNow was probably due to EDTA interference problems (21); Lot-to-lot variation for the methods is a concern (32); simple to be operated by untrained patient users who can obtain performances equivalent to that obtained by trained medical professional users (43)
A1cNow+	2.74% (low level)-4.02% (high level) (assumed total CV)	(9, 10)	Ranges from -12.0 to +21.9 mmol/mol (-1.1 to + 2%)	(9-14)	Device is wearable and can be used anywhere (14); provides a significant cost advantage to a patient who is responsible for fee-for-service and to primary care clinics that use the device for haemoglobin A1c determination (11); accessible, accurate and easy to use (10); A1CNow+ is a simple, portable, handheld device that is Clinical Laboratory Improvement Amendments waived, requires no calibration, and reagents need no refrigeration if used within 4 months (13)
B-Analyst	CV at low level HbA1c: 1.03-3.0%; CV at medium level HbA1c: 0.46-1.6%; CV at high level HbA1c: 0.78-1.3%; inter-assay CV: 1.4%	(16, 28)	Ranges from +1.2 to +2.1 mmol/mol (+0.11 to +0.19%)	(16, 28)	B-Analyst® may be suitable for the diagnosis and monitoring of diabetes according to the results shown in this study (16)

Cobas b 101	CV ranges from 1.2% to 2.8% (assumed total CV)	(15-17)	Ranges from -0.9 to +1.1 mmol/mol (-0.08% to +0.10%)	(16, 17)	Cobas B101 should not be used in regions where the prevalence of Hb AE is high unless the patient has been screened for this haemoglobin variant (16); with HbA1c values >10 the Cobas showed a strong proportional negative bias (17); provides rapid, accurate and highly precise measurements of HbA1c (15)
DCA 2000 (Withdrawn but may still be in circulation)	Within-run imprecision: 2.3-3.2%; (assumed total CV) 1.6-3.93% (low level) to 2.4-3.15%; within-site imprecision: 3.6%	(47-51)	Ranges from -10.2 to +3.0 mmol/mol (at HbA1c 5%) (-0.93 to +0.27%)	(47, 50-54)	Can be used to provide a rapid estimate of HbA1c upon which decisions on changes to treatment can be based at diabetic clinics (33); instrument was used without difficulty by four different operators (50); DCA was simplest instrument to maintain (49); breakdown of POCT quality errors by test type: number of tests = 1236; number of defects = 8; defect, % of total tests = 0.65, quality error rates associated with POCT may be considerably higher than those associated with central laboratory testing (55)
DCA 2000+	Total CV: 3.4% (low level) and 7.3% (high level)	(19)	Ranges from -3.4 to +9.4 mmol/mol (at HbA1c 5%) (-0.31% to +0.86% l)	(19, 34, 56-60)	Analytical quality is comparable to that of hospital laboratory instruments (34)
DCA Vantage	Total CV ranges from 0.7-5-5%; within-run precision: 1.55-2.53% (low level) to 2.29-2.9% (high level); between-day precision: 1.42-2.3% (low level) to 2.4-3.9% (high level)	(16, 20-23, 26)	Ranges from -5.0 (at HbA1c 6.5%) to +3.5 mmol/mol (-0.455% to + 0.316%)	(16, 20-26)	Lot number-dependent performance (20); device is small and can be installed on a bench or on a table; user-friendly, with good ergonomics (23).

InnovaStar	CV ranges from 1.2% to 4.5% (low level) and from 1.2% to 3.9% (high level) (assumed total CV)	(16, 21, 27)	Ranges from -5.1 to -1.7 mmol/mol (-0.47% to -0.158%)	(16, 21)	Needs to be calibrated and certified with fresh patient samples instead of frozen material (16); users were satisfied with the user manual; InnovaStar HbA1c instrument requires users with laboratory experience; The quality goal for accuracy (≥95% of results deviating ≤±10% from the results of the comparison method) was neither fulfilled by the hospital laboratory (84 and 68%), nor by the two primary health care centres (73 and 88%). For results >37 mmol/mol, 94% of the venous results had a deviation less than ±10% in hospital. The internal quality control material from the manufacturer was assessed as satisfactory (27)
SD A1c Care	SI units (mmol/mol): at HbA1c 37 and 80: CV 4.5% and CV 3.2%; NGSP units (%): at HbA1c 5.5 and 9.5: CV 2.7% and CV 2.6%	(29)	At HbA1c 5%: 0.4 mmol/mol (0.0387%)	(29)	Showed an optimal precision in the field; results of the SD A1cCare instrument correlated significantly with those of the Variant II Turbo instrument (29).

Guidelines and Recommendations

The WHO recommends the use of HbA1c for the diagnosis of type DM at an HbA1c of 48 mmol/mol (6.5%). In addition a value less than 48 mmol/mol (6.5%) does not exclude diabetes diagnosed using glucose tests, there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below this cut point (3). The WHO guidance stipulates "stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement."

In the UK guidance on implementing the WHO recommendations, HbA1c is also recognised as a diagnostic tool for type 2 DM only. The guidance details a number of conditions where HbA1c should not be used such as in suspected type 1 DM, children and young adults, pregnancy, renal failure and anaemia (2, 61).

NICE guidance PH38, Type 2 diabetes: prevention in people at high risk re-iterates the WHO guidance and also suggests that an HbA1c value of the range 42–47 mmol/mol (6.0–6.4%) is considered to be 'high risk'. The general guidance for type 2 DM is currently under review.

Research Questions:

Many of the studies included in this Horizon scan were performed in laboratory settings by laboratory trained professionals. A number of studies for the A1cNow, the DCA family and the Affinion were conducted by non-laboratory trained staff in a range of clinical settings such as the GP practice or pharmacy led clinics (11-14, 39, 40, 50, 58), however only one study has compared the performance of analysers between trained laboratory staff and non-laboratory trained staff. Whilst there is no clear difference in performance of the analysers a systematic review and meta-analysis of performance in the two user groups is warranted as well as trials in both primary and secondary care settings, to determine the accuracy and precision of the instruments in the hands of the intended users as opposed to trained laboratory professionals.

Additionally studies which further assess the cost:benefit ratio of using POCT devices compared with laboratory services, in primary care settings are warranted. It is important to consider if the use of POCT improves outcomes for people when diagnosing Type 2 DM.

The studies included address the analytical performance of POCT devices in various settings with various users, however they do not address whether the use of these devices will actually lead to an improvement in patient care or patient outcomes over the use of laboratory based testing.

Suggested next steps:

- Studies to assess the performance, in relation to quality targets, of a range of POCT devices for the diagnosis of Type 2 DM, in the hands of non-laboratory trained staff. The quality targets are still to be determined but are likely to be in line with IFCC guidance.
- Studies to assess patient outcomes and patient satisfaction when POCT devices are used as an alternative to laboratory testing, for the diagnosis of Type 2 DM in primary care.

Expected outcomes:

HbA1c has a lower biological variation than glucose and is a more stable analyte for the diagnosis of diabetes. If, in the future, any POCT devices for HbA_{1c} are demonstrated to be sufficiently accurate and precise to meet expected quality targets (7) then it may be possible to use these devices as alternatives to laboratory testing for the identification of people with type 2 DM. This is likely to be of benefit to those undertaking the National Health Checks in primary care.

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