

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of DG14: Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point-of-care coagulometers

This guidance was issued in September 2014.

The review date for this guidance is September 2017.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Recommendation

Produce a technical supplement and transfer the guidance to the 'static guidance list' with a post-publication update to the recommendations to reflect that the InRatio2 PT/INR monitor is not available to the NHS.

The suitability of newer technologies identified during the review will be explored for a relevant NICE advice output.

At the Guidance Executive meeting of 14 November 2017 it was agreed that no consultation on the recommendation was required. A list of the options that were considered, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Rationale

No evidence was identified which is likely to change the underlying recommendation but there have been changes to the available technologies which can be effectively and efficiently summarised using technical and advice products.

3. Implications for other guidance producing programmes

No overlaps have been identified.

4. Original objective of guidance

To assess the clinical and cost effectiveness of point-of-care coagulometers (the CoaguChek XS system and the INRatio2 PT/INR monitor) for self-monitoring coagulation status.

5. Current guidance

Adoption recommendations

Recommendation 1.1

The CoaguChek XS system is recommended for self-monitoring coagulation status in adults and children on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease if:

- the person prefers this form of testing and
- the person or their carer is both physically and cognitively able to self-monitor effectively.

Recommendation 1.2

The InRatio2 PT/INR monitor is recommended for self-monitoring coagulation status in adults and children on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease if:

- the person prefers this form of testing and
- the person or their carer is both physically and cognitively able to self-monitor effectively.

Although there is greater uncertainty of clinical benefit for the InRatio2 PT/INR monitor than for the CoaguChek XS system, the evidence indicates that the precision and accuracy of both monitors are comparable to laboratory-based INR testing.

Recommendation 1.3

Patients and carers should be trained in the effective use of the CoaguChek XS system or the INRatio2 PT/INR monitor and clinicians involved in their care should regularly review their ability to self-monitor.

Recommendation 1.4

Equipment for self-monitoring should be regularly checked using reliable quality control procedures, and by testing patients' equipment against a healthcare professional's coagulometer which is checked in line with an external quality assurance scheme. Ensure accurate patient records are kept and shared appropriately.

Recommendation 1.5

For people who may have difficulty with or who are unable to self-monitor, such as children or people with disabilities, their carers should be considered to help with self-monitoring.

6. New evidence

The search strategy from the original diagnostics assessment report was re-run on Embase, Ovid MEDLINE, Web of Science, Cochrane Libraries, ClinicalTrials.gov, WHO ICTRP, HMIC, PubMed. References from 2013 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Companies were asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. Specialist committee members for this guidance topic were also consulted and asked to submit any information regarding changes to the technologies, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. Details of ongoing and unpublished studies are presented in Appendix 2.

6.1 Technologies

The INRatio2 PT/INR monitor (Alere Ltd)

Diagnostics guidance 14 was updated after publication (in October 2016) to note that "NICE is aware that the INRatio2 PT/INR monitor (Alere Ltd) had been withdrawn from the market and was not available to the NHS". This text is presented on the overview page of diagnostics guidance 14.

Alere have confirmed that the INRatio 2 PT/INR is still not available to the NHS and that no replacement device has been released.

The CoaguChek XS system (Roche Diagnostics)

The CoaguChek XS has been replaced by the CoaguChek INRange meter, which was launched in the UK in May 2017. The XS version of the device is still supported by the manufacturer and the testing strips are still available. The CE mark for the XS version has not changed since diagnostics guidance 14 published. A clinical expert noted that there have been minor changes to the XS test strips.

The company have stated that the CoaguChek INRange meter uses equivalent testing technology to the XS version, but has enhanced user functionality features. These include a colour screen, the ability to set reminders on the meter, add

comments to individual results and new connectivity options [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

The company provided a white paper comparing the performance of the INRange and XS CoaguChek versions. INR (international normalised ratio) values produced by the 2 versions are strongly positively correlated ($r=0.99$). The relative mean difference between XS and INRange was 1.3%, with a slope of 1.00 and intercept of 0.00. The white paper also lists technical specifications for the two versions, identifying that there are no differences in measurement time, measurement range and battery operation.

Costs related to the CoaguChek XS used in diagnostics guidance 14 and costs for the CoaguChek INRange provided by the company are shown in table 1.

Table 1 Device and material costs of CoaguChek

Component	CoaguChek XS (from diagnostics guidance 14)	CoaguChek INRange
Device cost	£299	[REDACTED]
Test strips (per unit)	£2.81	[REDACTED]
Lancets (per unit)	£ 0.04	[REDACTED]

Additional technologies

Two additional devices that can be used for patient self-monitoring of coagulation status have been identified: the CoagMax (Microvisk) and the microINR (iLine Microsystems). The products are potentially suitable for a NICE medtech innovation briefing and this will be explored.

CoagMax (Microvisk)

The Microvisk website states that the CoagMax is a point-of-care PT/INR monitor that can be used for at-home patient testing. The device uses a cantilever which pulses within the blood sample and measures resistance. The cantilever and Micro Electro Mechanical System (MEMS) chip are embedded in a disposable strip.

microINR (iLine microsystems)

The iLine microsystems website states that the microINR is intended for monitoring vitamin K antagonist oral anticoagulant therapy. The website also states that the device has a CE mark for patient self-testing. The technology is based on a

disposable chip which contains microfluidic technology for the testing of blood samples.

6.2 Clinical practice

The British Committee for Standards in Haematology has published [guidance on self-testing and self-management](#). This emphasises the importance of training in the use of the devices (as stated in diagnostic guidance 14, recommendation 1.3). Patient experience in a small sample of study participants has also been used to produce [recommendations for supporting patients who are self-managing](#).

The European Heart Rhythm Association's (EHRA's) [guidance on managing patients with cardiac tachyarrhythmias](#) reported that patient self-testing is "*...suitable for those who have a good understanding of their condition(s) and warfarin therapy, are able to follow potentially complex instructions and advice, have a means of routinely checking their INR in a valid and accurate manner (e.g. via a point of care device in their own home), and have clear lines of communication with the healthcare team (with instructions to titrate therapy or seek immediate help as required).*" The guidance also emphasises the role of carers for patients whose cognitive impairment might prevent them from effectively self-testing.

The EHRA guideline also highlights the emergence of newer therapies which are replacing warfarin, noting however that "*...warfarin therapy will remain central to the management of AF in many individuals for the foreseeable future.*" A clinical expert also suggested that the use of warfarin is slowly being replaced by other anticoagulants for non-valvar atrial fibrillation, and these do not need monitoring; therefore the requirement for these monitors in this setting is likely to diminish. However they also commented that there will continue to be a requirement to use warfarin in patients with mechanical valves and other complex conditions.

6.3 New studies

6.3.1 CoaguChek

An overview of 19 published studies and 1 conference abstract relating to the use of the CoaguChek device to monitor coagulation status, all published after diagnostics guidance 14, is presented below. The CoaguChek device is used in all studies (13 studies use the XS version, 5 use the XS plus and 2 use either the S or XS versions). No published evidence was identified on the CoaguChek INRange device. Testing was carried out in a self-testing environment unless otherwise specified.

Evidence on clinical and intermediate outcomes

RCTs

Dignan et al. (2013) compared use of CoaguChek (S or XS version) with usual care (standard management of warfarin control with regular lab tests and dose scheduling by GP, cardiologist or coagulation clinic) in 310 people on warfarin therapy in Australia. People in the usual care group spent a greater proportion of time outside their target therapeutic range (40.7% compared to 35.5% for CoaguChek; $p < 0.001$). The CoaguChek group had significantly fewer extreme INR values ($p = 0.03$) and smaller average deviation ($p = 0.02$) compared to the usual care group. Serious adverse events were not significantly different between the groups.

Davidson et al. (2015) carried out an un-blinded RCT in 103 patients (mean age 85.3 years) on warfarin therapy in Sweden. The authors compared CoaguChek XS Plus (tests administered by a community nurse) to usual care (district nurses taking blood by venipuncture for lab testing followed by dosing changes 24-hours later). The proportion of patients in their target therapeutic range did not differ significantly either between the groups or from baseline to study end (CoaguChek baseline 75.9% to study end 72.6%; usual care 75.2% to 72.9%). There were 2 warfarin related adverse bleeding events overall (1 in each group).

Observational studies

Several observational studies reported that use of the CoaguChek for monitoring increased the time in therapeutic range for patients (Bishop et al. 2014; Solvik et al. 2015; Tamayo Aguirre et al 2016). da Silva et al. (2016) reported no significant increase in patient's time in therapeutic range in a cohort using the CoaguChek XS for self-testing over 1 year.

Bishop et al. (2014) reported no significant difference in major bleeding and thrombotic events between cohorts monitored using CoaguChek (testing was done either by patients or a pharmacist, and patients received dosing instructions from an anticoagulation clinic) and usual care in a retrospective study of patients in the US. Christensen et al. (2016) reported a retrospective study on a Danish cohort, including 3075 participants conventionally managed by laboratory testing in an anticoagulation clinic and 615 participants using CoaguChek self-management. After 5 years, there was no significant difference in the occurrence of thromboembolic events (hazard ratio 0.91; 95%CI: 0.66-1.24) or major bleeding events (hazard ratio of 0.83; 95%CI: 0.56-1.22). All-cause mortality was significantly lower in the CoaguChek group (1.08% versus 2.47%; hazard ratio 0.49; 95%CI: 0.34-0.71).

Tamayo Aguirre et al. (2016) reported a prospective study of a Spanish multi-centre cohort made up of 666 people on oral anticoagulant therapy; 333 were self-management patients using CoaguChek XS and the other 333 were usual care

patients, with treatment based on clinic visits and an undisclosed lab test. CoaguChek significantly improved quality of life scores, with satisfaction, self-efficacy in disease management and psychological stress scores all above baseline scores ($p < 0.001$). Chen et al. (2015) reported that a cohort of patients in China preferred testing with the CoaguChek fingertip blood collection method when compared to venepuncture (CoaguChek tests were carried out by professionals). da Silva et al. (2016) found no significant differences in patient-reported quality of life outcomes between CoaguChek in a patient self-testing environment and usual care in a cohort of 25 patients in Brazil.

Performance of point-of-care coagulometers

Twelve identified studies evaluated CoaguChek (using either the XS or XS Plus) against a laboratory test standard (Araujo et al. 2014; Baker et al. 2017; Benade et al. 2016; Biedermann et al. 2015; Dillinger et al. 2016; Fu et al. 2014; Hur et al. 2013; Kako et al. 2017; Kalcik et al. 2017; Riva et al. 2017; Tafoya et al. 2017; Vasquez et al. 2017). CoaguChek testing was carried out by professionals in all studies, and the laboratory test used as comparator varied between studies.

The studies generally reported good agreement of INR values produced by CoaguChek and laboratory tests. However, some studies reported that CoaguChek tended to overestimate INR at higher values, as confirmed by the laboratory tests. Vasquez et al. (2017), Hur et al. (2013) and Kako et al. (2017) reported increased disagreement at $\text{INR} \geq 2.0$; Fu et al. (2014), Vasquez et al. (2017) and Baker et al. (2017) at $\text{INR} > 3.0$; Araujo et al. (2014) and Benade et al. (2016) at $\text{INR} > 3.5$; Biedermann et al. (2015) at $\text{INR} > 4.0$; Tafoya et al. (2017) at $\text{INR} > 4.5$; and Kalcik et al. (2017) at $\text{INR} > 5.0$.

Nine of the studies used a Stago STAR lab test as a reference standard (Baker et al. 2017; Benade et al. 2016; Biedermann et al. 2015; Dillinger et al. 2016; Hur et al. 2013; Kako et al. 2017; Kalcik et al. 2017; Tafoya et al. 2017; Vasquez et al. 2017). Baker et al. (2017) found that agreement was stronger between CoaguChek and the Siemens BCS laboratory test ($\text{INR} < 3.0$, $\kappa = 0.84$; $\text{INR} \geq 3.0$, $\kappa = 0.70$) than it was between CoaguChek and Stago STAR ($\text{INR} < 3.0$, $\kappa = 0.62$; $\text{INR} \geq 3.0$, $\kappa = 0.10$). Tafoya et al. found improved correlation between CoaguChek and the IL TOP laboratory test ($r = 0.911$) compared to correlation between CoaguChek and Stago STAR ($r = 0.783$). The Stago STAR test uses rabbit brain thromboplastin while CoaguChek, IL TOP and Siemens BCS tests use human recombinant thromboplastin.

The studies also assessed clinical disagreement between CoaguChek and laboratory tests; that is, when a difference in INR measured by the tests would result in different dosing decisions being made. This varied between studies, from 0% of cases (Riva et al, 2017), 7% (Benade et al, 2016), 9.7% (Fu et al, 2014), 10% (Dillinger et al, 2016), 10.5% (Kako et al, 2017), 15.7% (Kalcik et al, 2017), 17.8% (Hur et al, 2013), 21.5% (Biedermann et al, 2015) to 49% (Vasquez et al, 2017).

Economic evidence

Five studies were identified that reported economic evidence on INR self-testing, plus 2 publications resulting from the original diagnostics assessment report for diagnostics guidance 14.

Craig et al. (2014) is the published version of an economic model of INR self-monitoring which was provided by Roche (the manufacturer of CoaguChek XS) and used in the original diagnostics assessment report to inform the structure of the economic model. Craig et al. (2014) reports the results of a Markov model comparing self-testing and self-management using the CoaguChek XS to usual care in patients with atrial fibrillation and mechanical heart valves over a 10-year period. The results suggested that self-monitoring would save £1,187 per person compared to usual care over a 10-year period

Gaw et al. (2013) reported that home monitoring using CoaguChek XS for infants and children managed via the Haematology department at a tertiary paediatric centre in Australia saved a total of 1 hour 19 minutes per INR test compared to attending anticoagulation clinics. This had a cost saving to society of AUD \$66.83 (£33.13 in September 2017) per INR test compared to standard care. An RCT comparing use of the CoaguChek XS with usual monitoring routines in Sweden over 12 months (Davidson et al. 2015; described above) reported that use of the CoaguChek produced a saving of SEK 624 (£51 in September 2017) per patient per year.

Gallagher et al. (2015) conducted an economic evaluation alongside an RCT of pharmacist-supervised patient self-testing of warfarin therapy compared with routine care in Ireland (hospital based management). Over a 6-month period, patient self-testing resulted in an incremental cost of €59.08 (£53 in September 2017) per patient in comparison with routine care; with patients spending a significantly longer time in therapeutic range in the patient self-testing arm. The authors reported that patient self-testing was the dominant strategy if the analysis was conducted from a societal perspective, and that pharmacist-led patient self-testing provided significant increases in anti-coagulation control for a minimal increase in cost.

A cost utility study from the USA (Phibbs et al. 2016) reported that an average utility gain of 0.09 QALYs per year for once-weekly patient self-testing came at an additional cost of less than \$1000 over 2 weeks, resulting in an incremental cost-effectiveness ratio of \$5,566 (£4,028 in September 2017).

6.3.2 Additional technologies

CoagMax (Microvisk)

No published studies on the CoagMax have been identified. Two ongoing studies have been identified ([NCT02319109](#) and [NCT02355730](#)) which focus on the development of the device. No data have been posted from these studies.

microINR (iLine microsystems)

Several studies involving the microINR have been identified, reported in 2 published articles (Van Den Besselaar et al. 2015 and Larsen et al. 2017) and 3 conference abstracts (Corno et al. 2014; Dirienzo et al. 2014 and Paniccia et al. 2015). In all of the studies the tests were carried out by professionals and none evaluated the device in a self-testing environment. Studies show mixed results on the performance of the test.

Van Den Besselaar et al. (2015) reported that microINR values were significantly different to a laboratory standard when INR was <2.5 (bias of -10.9%) and >2.5 (bias of -16.2%). Larsen et al. (2017) evaluated the microINR in patients from 3 outpatient and primary health care centres in Norway (n=176). MicroINR imprecision, as measured against laboratory tests, was 6% in the outpatient clinic and 6.3% in the primary health care centres, which did not meet the required quality goal for imprecision defined by SKUP (Scandinavian evaluation of laboratory equipment for primary health care).

Corno et al. (2014) reported that microINR results for INR were significantly positively correlated with INR results from laboratory tests ($p<0.0001$). Dirienzo et al. (2014) reported that the microINR was well correlated with laboratory tests for prothrombin testing as measured by INR (Pearson's coefficient 0.8817 [95% CI: -0.841 to 0.723]). Paniccia et al (2015) reported that microINR and laboratory testing were significantly positively correlated for INR ($p<0.001$). The authors also found significant correlations between microINR and lab tests for different ranges of INR (<2.0 , 2.0 to 3.0, 3.0 to 4.0, and >4.0).

7. Summary of new evidence and implications for review

Studies that have reported after publication of diagnostics guidance 14 in general support use of CoaguChek for patient self-testing. Two RCTs were identified; 1 of which found that use of CoaguChek increased the proportion of patients within their target therapeutic range and 1 which reported no effect of the device on time in target therapeutic range. Several observational studies also reported that use of the CoaguChek for monitoring increased time in therapeutic range for patients. Studies found that use of CoaguChek did not result in higher incidence of adverse events and that use improved patient quality of life. Identified cost-effectiveness studies support the recommendation in diagnostics guidance 14 that CoaguChek is cost effective.

A new version of the CoaguChek device has been released since publication of diagnostics guidance 14. Data provided by the company shows likely equivalence of INR results produced by the CoaguChek XS system (which was included in diagnostics guidance 14) and the CoaguChek INRange which has replaced this device. [REDACTED]

[REDACTED]

Two new devices that could be used for patient self-monitoring of coagulation status have been identified. However, no data on the clinical or intermediate outcomes arising from use of these devices have been identified.

In conclusion, the evidence base and clinical environment has not changed to an extent that is likely to have a material effect on the adoption recommendations in the existing guidance; it is therefore suggested that the guidance is transferred to the static list after being amended to reflect that the InRatio2 PT/INR monitor is not available to the NHS.

8. Implementation

The manufacturer of the CoaguChek devices have stated that use is widespread across the NHS. [REDACTED]

[REDACTED]

9. Equality issues

No new equality issues have been identified since the publication of the guidance.

Paper sign off by: Mark Campbell, Associate Director, 3 November 2017

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Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE’s work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE’s work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – ‘Yes/No’
Transfer the guidance to the ‘static guidance list’	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE’s work programme.	Yes
Defer the decision to review the guidance to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

- [Venous thromboembolic diseases: diagnosis, management and thrombophilia testing](#) (2015) NICE guideline CG144
- [Atrial fibrillation: management](#) (2014) NICE guideline CG180
- [Atrial fibrillation](#) (2013) NICE quality standard 93

In progress

- [Venous thromboembolism – reducing the risk \(full update\)](#) NICE guideline. Publication expected March 2018

Referred - Qs and CGs

None identified.

Suspended/terminated

None identified.

Registered and unpublished trials

Trial name and registration number	Details
Patient-Centered Anticoagulation Self-Monitoring in Minority Patients NCT02776566	Open-label randomised trial comparing usual care through pharmacist managed anticoagulation clinic and patient self-monitoring. CoaguChek used to assess coagulation status. Primary outcome measure: percent time in therapeutic range. Secondary outcome measures include: treatment related quality of life, self-testing competency and self-testing accuracy. Status: Recruiting

Trial name and registration number	Details
Accuracy of CoaguChek XS in Patients With Antiphospholipid Antibody Syndrome NCT02139072	Observational case-control study design. Two cohorts: patients with Antiphospholipid Antibody Syndrome (APL) have their INR measured using CoaguChek XS or with venous lab draw. Primary outcome: Comparison of INR obtained by CoaguChek XS to INR obtained from venous lab draw. Difference of +/- 0.5 considered significant. Status: Study has been completed (no results posted).
Blood Donation for the Development and Optimisation of the Second Generation Microvisk International Normalized Ratio (INR) Testing System for the Measurement of Prothrombin Time (PT)/INR in Patients on Warfarin Therapy. NCT02355730	Recruitment status unknown.
A Prospective, Single-Center Study, in Healthy Volunteers to Establish a PT/INR Reference Interval for the Microvisk INR Test System NCT02319109	Status: Study has been completed (no results posted).

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