

Spartan RX point-of-care CYP2C19 test to guide treatment in acute coronary syndrome

Medtech innovation briefing

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Summary

- The **technology** described in this briefing is the Spartan RX point-of-care DNA test. It is used to detect mutations in the CYP2C19 gene. This can help guide treatment of people with acute coronary syndrome who have a percutaneous coronary intervention (PCI).
- The **innovative aspects** are that the technology is a point-of-care test that provides results at the time of PCI without the need for follow-up hospital appointments.
- The intended **place in therapy** would be in addition to standard care or in place of lab-based CYP2C19 genotyping for people with acute coronary syndrome who have PCI.
- The **main points from the evidence** summarised in this briefing are from 6 studies (2 randomised controlled trials, 3 prospective cohort studies, and a report on a subset of 1 of the randomised controlled trials) including a total of 3,930 patients having or intending to have PCI. They show that genotype-guided antiplatelet therapy is non-

inferior to standard treatment for thrombotic events and has a statistically significantly lower incidence of minor bleeding. They show that using Spartan RX is clinically feasible, with results usually available 1 hour to 2 hours after collection.

- **Key uncertainties** around the evidence or technology are that guided antiplatelet therapy using CYP2C19 genotyping is not currently recommended as standard practice in the NHS, and that it has not been shown to be better than standard care for thrombotic outcomes (myocardial infarction, stent thrombosis, stroke or major bleeding). It is also not clear what impact repeat testing with Spartan RX, which may be needed if results are not conclusive, may have on the timing of treatment decisions and resource use.
- The **cost** of the Spartan RX test is £10,000 for the platform plus £175 per test for consumables (excluding VAT).

The technology

Spartan RX CYP2C19 System (Genomadix) is a point-of-care DNA test used to detect mutations in the CYP2C19 gene, specifically the *2, *3 and *17 alleles. CYP2C19 gene mutations impair response to medicines metabolised by CYP2C19, such as the antiplatelet drug clopidogrel. Clopidogrel is commonly prescribed after percutaneous coronary interventions (PCIs). People with an impaired response to clopidogrel can go on to have adverse cardiovascular events. Testing with Spartan RX aims to identify these people based on their CYP2C19 genotype. They can then be offered alternatives to clopidogrel.

The technology comprises:

- Spartan RX Platform. This contains the Spartan RX Analyser or thermal cycling instrument for polymerase chain reaction (PCR) amplification, the Netbook user interface, and a printer and barcode scanner for automatically entering collection kit lot numbers.
- Spartan transport system. This is an insulated transport bag containing a polystyrene box and a cold block designed to keep collection kits and samples cold before analysis.
- Spartan RX assays (sample collection kit and external control kit). This contains all the consumables needed to determine CYP2C19 genotype, including a reagent tube, a buccal swab, and a pouch with labelling information and a barcode. There are 3

different colour-coded collection kits to be used (one each for CYP2C19 *2, *3 and *17 genotype assays).

The test uses a buccal sample taken using a buccal swab. Samples are inserted into a reagent tube and placed into the transport system until the sample is ready to be analysed. The samples are then run on the Spartan RX system, which combines and automates DNA extraction, PCR amplification, and fluorescence-based detection of CYP2C19 alleles.

The test is not intended to be used to predict drug response or non-response. The test result should be used together with standard clinical decision making alongside routine monitoring.

The company has released a successor to the Spartan RX device called the Spartan Cube. The Spartan Cube differs from Spartan RX in that the 3 reaction tubes are integrated into a single test cartridge, the swabs and test cartridges are packaged separately, and the DNA analyser device is smaller.

Innovations

The innovative aspect of the technology is that it is a point-of-care test. The test can be done at the time of PCI and results can be available within 55 minutes. The test does not require any specialised laboratory experience or training, and can be used directly by attending healthcare professionals. The test does not require sample preparation and results are given without the need for data interpretation. Current CYP2C19 genotyping tests are processed in central laboratories and require a follow-up appointment to receive the results and adjust the patient's therapy, if needed.

Current care pathway

Patients presenting with acute coronary syndrome who are having PCI are typically prescribed dual antiplatelet therapy, consisting of aspirin and a P2Y₁₂ receptor inhibitor, to prevent major adverse cardiovascular events. Antiplatelet therapy is started before or at the time of PCI and continued for 12 months afterwards.

People with ST-segment elevation myocardial infarction (STEMI) should be offered the P2Y₁₂ receptor inhibitors prasugrel or ticagrelor with aspirin. Clopidogrel is recommended when ticagrelor and prasugrel are not available or are contraindicated.

People with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI) having PCI should also be offered prasugrel or ticagrelor with aspirin.

There are no explicit recommendations around routine CYP2C19 genotype testing or genotype-guided therapy in these patients, and no particular tests have been recommended.

The following publications have been identified as relevant to this care pathway:

- [Acute coronary syndromes \(NICE guidance in development, expected publication date: November 2020\)](#)
- [European Society of Cardiology guidelines on acute myocardial infarction in patients with ST-segment elevation](#)
- [NICE technology appraisal guidance on prasugrel with PCI for treating acute coronary syndromes](#)
- [NICE guideline on acute management of STEMI](#)
- [NICE guideline on early management of unstable angina and NSTEMI](#)
- [NICE technology appraisal guidance on ticagrelor for the treatment of acute coronary syndromes.](#)

Population, setting and intended user

The population is people with acute coronary syndromes having PCI who need antiplatelet therapy. In 2017 to 2018, 102,258 PCI procedures were done in 118 PCI centres in the UK ([National Audit for PCI, 2019](#)).

Clopidogrel is a widely prescribed P2Y₁₂ receptor inhibitor for dual antiplatelet therapy in people having PCI, although 2% to 14% of the population do not metabolise it well. This is primarily because of mutations in the CYP2C19 gene, and Spartan RX aims to help guide treatment in these people. The test would be done in secondary care by an interventional cardiologist at the time of the PCI procedure.

Costs

Technology costs

There is a capital equipment cost of £10,000 for the platform plus £175 per test for consumables (excluding VAT). Spartan RX and cube products are priced similarly.

Costs of standard care

Standard care involves antiplatelet therapy without the use of CYP2C19 genotype testing.

Resource consequences

Spartan RX is not yet used in the NHS. If adopted, Spartan RX would initially cost more than standard care, which does not currently use CYP2C19 genotype testing. However, a tailored antiplatelet approach using the test may be resource releasing if genotype-guided therapy using the test leads to improved outcomes for patients (such as a reduced incidence of acute stent thrombosis) compared with prescribing clopidogrel empirically or selecting an alternative antiplatelet agent. This is not fully supported by the available evidence. There is evidence of a reduced incidence of minor bleeding, and non-inferiority to standard therapy for thrombotic events. But Spartan RX has not been shown to be better than standard therapy in terms of reducing thrombotic events. The company says that the technology is designed to be used without extensive laboratory training but it does provide free training if needed.

Regulatory information

Spartan RX is CE marked as a class I in vitro diagnostic.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Acute coronary syndromes become more prevalent with increasing age, and incidence is

higher in men. CYP2C19*2 and CYP2C19*3 mutations are more common in people of Asian family origin who are more likely to be poor metabolisers of clopidogrel. Age, sex and race are protected characteristics under the Equalities Act.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Six studies are summarised in this briefing involving 3,930 patients. Studies include 2 randomised controlled trials, 3 prospective cohort studies, and a study reporting on outcomes from a subset of people enrolled in 1 of the randomised controlled trials.

The clinical evidence and its strengths and limitations is summarised in the next section on overall assessment of the evidence.

Overall assessment of the evidence

The evidence for Spartan RX suggests that the test is easy to use and clinically feasible. In most of the studies, the test could be done by a healthcare professional after short training and results were usually available within 1 hour to 2 hours after sample collection. Some studies reported that another sample had to be taken because of inconclusive results but it is not clear if this delayed treatment decisions or patient discharge. This highlights a potential need for extra training, particularly in taking time-sensitive buccal swabs.

The evidence suggests the test may mean clopidogrel is prescribed less often to people who poorly metabolise it because of their CYP2C19 genotype. But it does not show if treatment decisions made using the Spartan RX test alone significantly improve clinical outcomes for patients.

None of the included studies were done in the UK, and it is likely that clinical practice at

the study sites varied. Therefore, the generalisability of the evidence to the NHS may be limited. No studies directly compared Spartan RX with other genotyping methods (such as TaqMan StepOnePlus assay) in a clinical setting so it is unclear if the test has advantages over laboratory-based testing, especially in centres where batchwise genotyping is routinely done.

Claassens et al. (2019)

Study size, design and location

Randomised, open-label trial involving 2,488 patients having primary percutaneous coronary intervention (PCI) with stent implantation at 10 European sites (8 in the Netherlands, 1 in Belgium and 1 in Italy).

Intervention and comparator(s)

Intervention: P2Y12 inhibitor therapy based on early CYP2C19 genetic testing (genotype-guided group).

Comparator: standard treatment with either ticagrelor or prasugrel (standard treatment group).

Key outcomes

At 12 months, adverse clinical events (death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding as defined by Platelet Inhibition and Patient Outcomes criteria) occurred in 5.1% (n=63) of patients in the genotype-guided group and in 5.9% (n=73) of patients in the standard treatment group. CYP2C19 genotype-guided P2Y12 inhibitor therapy (in which patients without the CYP2C19 gene mutation had clopidogrel) was shown to be non-inferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events ($p < 0.001$; non-inferiority margin of 2% points for the absolute difference). Superiority analysis did not support the superiority of genotype-guided therapy (hazard ratio, 0.87; $p = 0.40$). Genotype-guided therapy was associated with a lower incidence of bleeding (122 events [9.8%] compared with 156 events [12.5%]; $p = 0.04$).

Strengths and limitations

It was a randomised multicentre study but had an open-label design so may be subject to bias. None of the study centres was based in the UK so generalisability of the results to the NHS is uncertain. The incidence of the primary combined outcome was lower than anticipated. Not all patients were genotyped using the Spartan RX test – TaqMan StepOnePlus assay at a central laboratory was also used. The company provided the Spartan RX system and reagents free of charge.

Bergmeijer et al. (2018)

Study size, design and location

Feasibility study reporting on data from 2 projects in which CYP2C19 genotyping was used to tailor antiplatelet treatment in patients admitted with ST-segment elevation myocardial infarction (STEMI) or having a planned PCI.

The study included all 1,283 patients who enrolled in the POPular Genetics study between July 2014 and 8 December 2017. It also reported on data from the Popular Risk Score project (n=2,556), but outcomes have not been included here because genotyping was done using the TaqMan StepOnePlus assay only.

Intervention and comparator(s)

Intervention: CYP2C19 genotyping strategies (Spartan RX, in-hospital TaqMan genotyping or central laboratory testing).

No comparator.

Key outcomes

Results from the study suggest that it is feasible to have genotyping results available within 24 hours to 48 hours for most patients. In the POPular Genetics study, the median time between randomisation and genotyping result was 2 hours 24 minutes (2 hours 4 minutes for in-hospital TaqMan genotyping, 2 hours 16 minutes for Spartan RX genotyping and 52 hours 32 minutes for central laboratory testing). One Spartan RX test result did not match with TaqMan genotyping result, and 8% of people had an inconclusive result with Spartan RX.

Strengths and limitations

The study did not involve any UK centres so the generalisability to the NHS is uncertain. Not all genotyping in the POPular Genetics study was done using Spartan RX; on-site TaqMan genotyping was used by 1 centre (487 patients), on-site Spartan RX genotyping by 7 centres (411 patients) and shipment to the central laboratory was used by 6 centres (140 patients). The company provided the Spartan RX system and test kit to 7 centres involved in the POPular Genetics study.

Cavallari et al. (2018)

Study size, design and location

Prospective cohort study involving 931 patients having left heart catheterisation for suspected coronary disease with intent to have PCI in 1 US centre.

Intervention and comparator(s)

Intervention: Spartan RX CYP2C19 genotype testing.

No comparator.

Key outcomes

The median turnaround time for genotype test results was 96 minutes. Genotyping was unsuccessful for the initial sample in 14% of people (56 inconclusive results and 73 device errors). Of these people, 123 agreed to have samples recollected; 6 of these had multiple inconclusive results. Forty-two percent of people who were genotyped had PCI (n=392). Genotype results were available for 99% of PCI patients before discharge. At discharge, 17% of poor metabolisers, 41% of intermediate metabolisers and 50% of patients without the CYP2C19 gene mutation were prescribed clopidogrel (p=0.110). At 6 months, clopidogrel was prescribed in 0% of poor metabolisers, 51% of intermediate metabolisers, and 63% of patients without a CYP2C19 gene mutation (p=0.008 across groups; p=0.020 for poor metabolisers compared with patients without a CYP2C19 gene mutation).

Strengths and limitations

The study did not account for confounding factors that may have influenced the decision

to switch therapy, for example the affordability of treatment for patients and the presence of conditions that may increase bleeding risk. The study did not include a control group of patients not having genotyping. The study was done in 1 US centre so may not be generalisable to the NHS.

Zhou et al. (2017)

Study size, design and location

Laboratory validation study and a prospective cohort study involving 342 people who had had a PCI at 1 US centre.

Intervention and comparator(s)

Intervention: Spartan RX CYP2C19 test.

Comparator: Verigene CYP2C19 test (laboratory validation study only).

Key outcomes

In the laboratory validation study, results were consistent between both assays (100% accuracy); both tests showed a sensitivity and specificity of 100% when results were obtainable. Samples tested on Verigene CYP2C19 produced a 20% no call rate and 1 processing error, whereas Spartan RX accurately identified the genotype on all 36 specimens. Of the 342 patients tested with Spartan RX in a clinical setting, 14 samples had inconclusive results, 10 failed controls, and there was 1 instrument failure. Results were available after retesting for 12 of these patients; 1 patient declined a retest, and 1 had a second inconclusive result. Overall, 27% (n=99) of the patients had a CYP2C19 gene mutation.

Strengths and limitations

The laboratory validation used a small number of unique samples. The study did not compare Spartan RX with Verigene in a clinical setting. The study was done in a single US centre so may not be generalisable to the NHS.

Koltowski et al. (2017)

Study size, design and location

Single-centre pilot study reporting interim results from a randomised controlled clinical trial (ONside TEST project).

The study involved 50 people (aged between 18 and 75) with stable coronary disease scheduled for an elective PCI with stent implantation in 1 centre in Poland.

Intervention and comparator(s)

Intervention: Spartan CYP2C19 test (genotype-guided therapy) or phenotype testing with the VerifyNow P2Y₁₂ assay (phenotype-guided therapy).

Comparator(s): No genotype testing (standard treatment with aspirin and clopidogrel).

Key outcomes

Five (32%) patients in the genotyping arm and 2 (13%) in the phenotyping arm were identified as poor metabolisers of clopidogrel and were given a loading dose of prasugrel at least 2 hours before the scheduled PCI. Genotyping took 1 hour. The test had to be repeated for 2 patients because of inconclusive results. Periprocedural platelet reactivity (pharmacokinetic response) was significantly lower in the genotyping and phenotyping groups compared with the control group (80 platelet reactivity units [PRU], range 49.0, $p=0.01$; 36.5 PRU, range 47, $p=0.03$; 176 PRU, range 67.8; respectively). There were no differences in the prevalence of periprocedural myocardial infarction, myocardial biomarker leak, and risk of major bleeding and major adverse cardiovascular events at the 30-day follow up.

Strengths and limitations

The study involved a small number of patients and may have been underpowered for outcomes. It also had an open-label design because of the number of interventions over the course of the study. People in the control group had a longer duration of total vessel occlusion during intervention. The study was in Poland and so results may not be generalisable to the NHS.

Choi et al. (2016)

Study size, design and location

Prospective cohort study involving 119 people with acute coronary syndrome who had PCI with drug-eluting stents in a centre in Korea.

Intervention and comparator(s)

Intervention: Spartan RX CYP2C19 test.

Comparator: single nucleotide polymorphism (SNP) genotyping assay (TaqMan).

Key outcomes

Based on results from Spartan RX CYP2C19 genotyping, 3.3% of patients were classed as ultra-rapid metabolisers, 32.8% as extensive metabolisers, 45.4% as intermediate metabolisers, and 18.5% as poor metabolisers. There were 2 discrepancies (1.7%) with Spartan RX compared with SNP genotyping. The discrepancy appeared in the *17 allele analysis for both patients, and the result with Spartan RX was a false positive. The authors said that a false positive result for *17 allele could not affect the intermediate or poor metaboliser group (who were more likely to have thrombotic events) but it could affect ultra-rapid metaboliser group (who were more likely to have bleeding events).

Strengths and limitations

The study was done in Korea and so may not be generalisable to an NHS population.

Sustainability

The company has not submitted any sustainability claims.

Recent and ongoing studies

- Tailored antiplatelet therapy following PCI (TAILOR-PCI). ClinicalTrials.gov identifier: NCT01742117. Status: enrolling by invitation; expected completion date: April 2020. Indications: coronary artery disease, acute coronary syndrome, stenosis.

Interventions: clopidogrel (drug), ticagrelor (drug), ABI TaqMan assay (retrospective genotype testing), Spartan genotyping system (prospective genotype testing), smartphone (other). Countries: US, Canada, Korea and Mexico. Study results were presented on 28 March 2020 during the virtual [American College of Cardiology 2020 Scientific Session \(ACC.20\)/World Congress of Cardiology](#).

- [Bedside testing of CYP2C19 gene for treatment of patients with PCI with antiplatelet therapy](#). ClinicalTrials.gov Identifier: NCT01823185. Status: unknown; expected completion date: March 2016. Indications: coronary artery disease, myocardial infarction, heart disease, vascular disease, angina pectoris, cardiovascular disease, ischemia, infarction, embolism, thrombosis, chest pain. Interventions: clopidogrel (drug), ticagrelor or prasugrel (drug), genotyping using Spartan genotyping system will be carried out for all intervention groups. Country: Saudi Arabia. Associated publication: [Al-Rubaish et al. \(2020\)](#).

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Experts were aware of Spartan CYP2C19 genotype testing but none of the experts had used this technology before.

Level of innovation

Two of the experts felt that Spartan RX is innovative and a novel approach to antiplatelet therapy decision making for patients presenting with acute coronary syndromes. One highlighted that current standard care in the NHS does not use any form of genetic testing to guide antiplatelet therapy. One expert felt it was a minor variation compared with standard care and that they had not yet found a clinical need to use this type of testing. An alternative assay used to detect CYP2C19 polymorphism was identified by 2 of the experts. One of these experts added that this alternative assay requires a blood sample for analysis.

Potential patient impact

Two experts said that the potential for personalised antiplatelet therapy by identifying patients who are unlikely to have a response to clopidogrel was a key benefit of the technology. The potential benefits of genotype-guided antiplatelet therapy that were identified by the experts include reduced bleeding, as well as reduced incidence of myocardial infarction, stent thrombosis and death. One expert said that improved clinical outcomes may be associated with reduced hospital visits and hospital-based investigations and treatment. Patients at high risk of bleeding, patients at high risk of future ischemic complications and patients at high risk of stent thrombosis were identified by some of the experts as those who would benefit most from Spartan RX testing. One of the experts noted that the benefits would be limited to patients with stable angina having coronary angioplasty with stent implantation who have had prior issues with clopidogrel efficacy or tolerability.

Potential system impact

Two experts noted that testing with Spartan RX has the potential to reduce morbidity and mortality and the subsequent costs associated with treating bleeding and ischemic complications. One expert felt that system benefits would be limited to patients with stable angina having coronary angioplasty with stent implantation who have had prior issues with clopidogrel efficacy or tolerability. All of the experts said that Spartan RX test would be an addition to standard care. Two experts felt that the technology could provide cost savings in the long term, whereas another expert felt that the technology would cost more than standard care and was unlikely to reduce the use of resources. Two experts noted that each trust would need to buy the machine and the test kits needed for each patient. One of these experts added that the resource impact will be minimal, but that the company would need to train clinical staff on how to use the assay and interpret results. The other expert said that adopting the technology would have no effect on primary care or care setting because the test is done in the catheter lab or cardiac care unit (CCU) at the time of percutaneous coronary intervention (PCI) and is unlikely to need additional staff. Potential barriers to adoption identified by experts were technology costs, as well as the niche role that 1 expert thought the test would play in a small group of patients.

General comments

The experts noted that the technology was not yet used in the NHS and none of the

experts were aware of any centres using the test routinely. One expert said that test is relatively easy to undertake (buccal swap and automatic point-of-care device). One of the experts did not think the technology will play a major role managing acute coronary syndromes. But they thought it could have a role in around 5% of patients with stable coronary disease having PCI. One expert was concerned about the repeated sampling needed in a substantial number of patients because of inconclusive results. One expert felt that an adequately powered global randomised controlled trial would be needed to show improvement in all-cause mortality, cardiovascular mortality, stroke and myocardial infarction compared with standard care. Another expert highlighted that, given the regional differences in genotype frequency, data from UK-based studies would be useful. They also said that future studies that focus on high bleeding risk groups would be helpful.

Expert commentators

The following clinicians contributed to this briefing:

- Michael Mahmoudi, associate professor in interventional cardiology, University Hospital Southampton NHS Foundation Trust, did not declare any interests.
- Dr Nicholas Pegge, consultant cardiologist, Western Sussex Hospitals NHS Foundation Trust, consultancy for AstraZeneca: received honoraria for educational lectures on antiplatelet therapy between 2012 and 2019.
- Tim Kinnaird, consultant cardiologist, Cardiff and Vale University Health Board, did not declare any interests.

Development of this briefing

This briefing was developed by NICE. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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