# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Medical technology guidance

## Assessment report overview

## The VeriQ system for assessing graft flow during coronary artery bypass graft surgery

This assessment report overview has been prepared by the Programme team highlighting the significant findings of the assessment report. This overview includes key features of the evidence base and the cost analysis, any additional analysis carried out, additional information, uncertainties and key issues the Committee may wish to discuss. It should be read in conjunction with the sponsor's submission of evidence and with the assessment report. The overview formed part of the information received by the Medical Technologies Advisory Committee when it developed its recommendations on the technology.

This overview also contains:

Appendix A: Sources of evidence

Appendix B: Comments from professional bodies

Appendix C: Comments from patient organisations

Appendix D: Additional analyses

Appendix E: Additional submission information table

Appendix F: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

# 1 The technology

The VeriQ system (MediStim ASA) uses ultrasonography for the non-invasive assessment of graft blood flow during coronary artery bypass surgery. The

system uses transit time flow measurements (TTFM) to assess graft blood flow and check patency. The CE mark certificate describes the VeriQ system as a 'medical ultrasonic non-imaging flowmeter system'. The US Food and Drug Administration (2004) indicates the VeriQ system for the accurate measurement of transit time, blood volume, blood pressure, vascular resistance and doppler velocity flow during cardiovascular and vascular surgery, transplantation and neurosurgery. The VeriQ system helps with the planning of surgery and supports its successful accomplishment, allowing the detection and location of vessels during surgical procedures. Arterial stenosis can be detected and quantified using the doppler velocity profile. This evaluation focuses on use of the VeriQ system during coronary artery bypass surgery (CABG) to measure graft flow using transit time flow measurements.

The VeriQ system measures transit time volume flow and doppler flow velocity using specially designed probes. A microcomputer with a 19-inch touch screen mounted on a moveable trolley is used to control these probes and store their outputs. There are three VeriQ system configurations (VeriQ 2011, VeriQ 2111, VeriQ 4122) and these have different numbers of channels for TTFM probes, doppler probes, blood pressure and auxillary monitors. All configurations have at least two channels for TTFM. Only probes for TTFM (QuickFit probes) are considered as part of this evaluation.

The QuickFit probes (either PS or PQ probes) come in a range of different sizes and can be used to measure graft function after completion of the bypass graft. QuickFit Probes can be sterilised and reused (up to 30 times for PS probes and 50 times for PQ probes). All probes deliver a bidirectional ultrasound beam across a target graft vessel and the system analyses the return signal to calculate the blood flow through the vessel. Direction of flow is also indicated and this can be correlated with electrocardiography and arterial pressure traces obtained from connections to an existing physiological monitor.

A real-time flow curve is displayed together with mean flow (in millilitres per minute), pulsatility index and diastolic filling percentage. This information can be used to determine whether flow in the target graft vessel is adequate. If

these measurements and the flow curve suggest that graft flow is not adequate, the graft can be revised before the completing the procedure to ensure optimum flow in all grafted vessels. Each measurement is saved in a database and can be exported to the hospital's electronic patient records using a USB device. Hardcopy reports are available via the on-board colour printer.

# 2 Proposed use of the technology

## *2.1 Disease or condition*

The VeriQ system is intended for use in patients with coronary heart disease who are undergoing coronary artery bypass graft surgery. Coronary heart disease is caused by a build-up of fatty deposits in the walls of the coronary arteries which supply blood to the heart. This can lead to narrowing of the coronary artery lumen and may lead to angina, myocardial infarction and death. In CABG the narrowed part of the coronary artery is bypassed to restore adequate blood flow to the heart.

## *2.2 Patient group*

There are over 2.7 million people with coronary heart disease in the UK (over 1.6 million men and over 1 million women). The prevalence increases with age and is higher in men than in women. Surgical procedures that are used to treat coronary heart disease include percutaneous coronary intervention (PCI) and CABG. It is estimated that around 28,000 coronary artery bypass operations are performed in the UK each year.

## *2.3 Current management*

Coronary heart disease cannot be cured but the symptoms can be reduced and the functioning of the heart improved. People with coronary heart disease are advised to make lifestyle changes to modify risk factors, such as stopping smoking, eating healthily and exercising regularly. Drugs such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and statins can also be used to improve the functioning of the heart and control symptoms. If the

symptoms are not controlled by lifestyle changes and/or drugs, surgical treatment such as a PCI or CABG is considered.

The aim of CABG is to bypass the narrowed coronary artery using grafts and so increase the blood flow to the heart muscle. Grafts are created from blood vessels in the chest, arm or leg and are attached to the coronary artery beyond the blockage. The surgeon may use a heart-lung bypass machine to oxygenate the blood and maintain the circulation during the procedure. Alternatively, for an off-pump CABG the heart is left beating throughout the procedure.

Blockage or poor blood flow in the graft may be a significant cause of morbidity and mortality after the procedure. Assessment of graft flow during surgery is usually done by clinical assessment which typically involves visual assessment of the anastomosis and digital palpation. NICE has produced interventional procedure guidance on an alternative technique, 'Intraoperative fluorescence angiography in coronary artery bypass grafting' (NICE interventional procedure guidance 98). The guidance states that 'current evidence suggests that the procedure is safe enough for routine use in the evaluation of coronary artery bypass graft patency'.

## *2.4 Proposed management with new technology*

The VeriQ system is used by trained cardiac surgeons during CABG for assessing blood flow in new grafts and verifying graft patency. Its use does not significantly change the length of the procedure and it is not expected to change current clinical pathways.

Recent European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularisation have recommended evaluating the graft before leaving the operating theatre after CABG. The guidelines recommend a blood flow less than 20 ml/min and a pulsatility index greater than 5 as predicting technically inadequate grafts, mandating graft revision before leaving the operating theatre (Kieser et al. 2010).

### *2.5 Equality and diversity issues*

No equality and diversity issues were identified

# 3 Issues for consideration by the Committee

### *3.1 Claimed benefits*

The benefits to patients claimed by the manufacturer are:

- The VeriQ system should improve the outcomes of revascularisation procedures by reducing the risk of early graft failure and adverse events.

The benefits to the health system claimed by the manufacturer are:

- The VeriQ system may reduce hospital stay for some patients by reducing the incidence of complications during and after surgery. The additional cost of using the VeriQ system may be more than offset by the savings made from reducing the number of repeat procedures and treatments for other post-operative complications.

- Accurate documentation of graft blood flow will provide a useful tool for clinical goverance and audit.

### *3.2 Main issues*

- The evidence base for the VeriQ system comprises three studies. Two studies compared clinical outcomes in patients undergoing CABG and graft flow assessment with the VeriQ system with outcomes in patients not having flow assessment with the VeriQ system. One study investigated differences in parameter reading between the VeriQ system and another flowmeter. Additional evidence from 26 studies has also been assessed by the External Assessment Centre (EAC). This evidence describes the use of MediStim predecessor devices which use the same transit time flow measurement (TTFM) principle for assessment of blood flow during CABG.
- The EAC concluded that the evidence base suggests that transit time flowmetry using the VeriQ system is a valid and reliable method of assessing flow in coronary artery bypass grafts and in predicting early graft failure. The two clinical studies demonstrated that use of the VeriQ system in patients undergoing CABG reduces mortality and complications. The 26

studies on MediStim predecessor devices provide broad support that assessment of graft flow during surgery with TTFM improves surgical outcomes.

- Use of the VeriQ system depends on the commitment of the surgeon and their confidence in interpreting the flow values. Some of the earlier studies discussed which parameter values should be used to indicate graft revision. The ESC/EACTS guidelines, based on results from Kieser et al. (2010), give a graft flow of less than 20 ml/min and a pulsatility index greater than 5 as predicting technically inadequate grafts requiring revision before the patient leaves the operating theatre.
- The economic model is constructed to consider the cost savings of using the VeriQ system compared with clinical assessment to assess graft flow in all patients undergoing CABG. In the base-case analysis, the equipment costs are about £100 per procedure based on the VeriQ 2011 (£32,000) and an average use of 1.7 probes per procedure (£1582 per PS probe which is valid for 30 uses). The cost saving associated with the VeriQ system was £121 per patient in the base case. The sensitivity analysis identified the key drivers of cost saving to be the reduction in the use of the intra-aortic balloon pump (IABP) and the rate of peri-operative myocardial infarction associated with the use of the VeriQ system.
- There is some uncertainty about the base-case savings because the annual service cost for the VeriQ system over its lifetime has not been included. Including this cost in the base case reduces the cost savings to £111 per patient.
- The manufacturer's submission is based on all 28,000 patients undergoing CABG per year in the UK being scanned with the VeriQ 2011 system using the PS probe. Advice from expert advisers is that if surgeons are fully confident that the graft is sound they would not usually use TTFM but would probably use the VeriQ system when the clinical assessment is ambiguous. The EAC noted that further saving may be possible if only those grafts which are in doubt are scanned, however the cost implications of this scenario were not calculated.

# 4 The evidence

## *4.1 Summary of evidence of clinical benefit*

The evidence for the clinical effectiveness of the VeriQ system is based on three studies. Two were retrospective cohort observational studies that examined surgical outcomes and one was a comparative study that investigated differences in parameter values from the VeriQ system and another flowmeter. All patients in the studies were undergoing CABG and the studies were conducted in hospitals in Europe and Canada (with none conducted in the UK).

Kieser et al. (2010) evaluated TTFM with the VeriQ system as a tool to detect technical errors in arterial bypass grafts intra-operatively and to predict postoperative major adverse cardiac events in a retrospective case study in Canada. They assessed 1000 arterial grafts in 336 consecutive patients. Three parameters of transit time flow (pulsatility index, flow, and diastolic filling percentage) were measured in 990 (99%) of the grafts. A pulsatility index value of less than 5 was chosen as the principal measure of graft adequacy. Ninety-three percent (916/990) of grafts with pulsatility index less than or equal to 5 occurred in 277 patients (82%) and were found to be satisfactory. The remaining 74 (7%) grafts with pulsatility index greater than 5 occurred in 59 patients (18%) and were deemed suboptimal. However, grafts were revised only when an abnormal pulsatility index supported the otherwise suspected graft malfunction (abnormal ECG changes, regional wall motion abnormality on trans-oesophageal echocardiography or haemodynamic compromise). Twenty grafts (2%) suspected to be problematic were revised. Patients were divided into two groups: 277 (82%) with at least one graft with pulsatility index less than 5 and 59 (18%) with at least one graft with pulsatility index greater than 5. The incidence of major adverse cardiac events (recurrent angina, perioperative myocardial infarction, postoperative angioplasty, repeat surgery and/or perioperative death) was significantly higher in patients with a pulsatility index greater than 5 (10/59, 17%) than in patients with a pulsatility index less than 5 (15/277, 5.4%, $p = 0.005$). Mortality after non-emergency surgery was significantly higher in patients with a

pulsatility index greater than 5 (5/54, 9%) than in patients with a pulsatility index less than 5 (5/250, 2%, p = 0.02). Regression analysis showed that pulsatility index greater than 5, age (per 10 years) and admission status were all independent significant predictors of major adverse cardiac events. A multivariate logistic regression model showed that pulsatility index greater than 5 was a significant predictor of major adverse cardiac events (odds ratio = 4.23, 95% CI 1.7 to 10.6, p = 0.002) after controlling for admission status and age; that is, for a given admission status and age, the risk of major adverse cardiac events was 4.2 times higher when the pulsatility index was greater than 5. The authors concluded that a high pulsatility index (>5) predicts a technically inadequate arterial graft during surgery and also predicts early adverse events after surgery, particularly mortality, even if all other assessments during surgery indicate good graft quality.

Becit et al. (2007) investigated the detection of graft dysfunction during surgery by TTFM using the VeriQ system in a retrospective cohort of patients undergoing on-pump CABG in Turkey. The study compared surgical outcomes for two series of consecutive patients whose operations were performed by the same surgeons. The study group (n = 100) had TTFM during surgery and the control group (n = 100) did not. The patients' characteristics and risk factors before surgery were similar between the two groups. TTFM was done on 303 grafts in the study group of 100 patients. Indicators of poor flow were pulsatility index grater than 5 and diastolic filling percentage less than 50%. Three percent (9/303) of grafts in 9 (9%) patients were revised, and after revision all flow values and flow patterns improved.

Overall mortality was lower in the study group (0/100 versus 4/100, p < 0.05). There was no difference between the patient groups in investigation for bleeding (3/100 versus 3/100, p > 0.05) and deep sternal infection (1/100 versus 1/100, p > 0.05). However, the incidence of intra-aortic balloon pump insertion for low cardiac output was significantly lower in the study group (1/100 versus 7/100, p < 0.05). Also peri- and post-operative mycocardial infarction was lower in the study group (0/100 versus 5/100, p < 0.05). The

authors believed that results suggested that detection of graft dysfunction during surgery by TTFM improved surgical outcomes.

Nordgaard et al. (2010) investigated the variation in pulsatility index measurement between two different flowmeters (VeriQ and Transonic) and examined whether increase in filtering of the flowmeter signals influences flow curves and pulsatility index. The VeriQ and Transonic flowmeters have different default filter settings of 10 Hz and 20 Hz respectively. The filter settings influence the smoothing of the waveform and may influence the measured PI.

Flow patterns in 19 cases recorded simultaneously by both flowmeters in the same CABG procedure were analysed and showed that the Transonic device provided systematically lower PI values than the VeriQ system (mean ± SD: 1.8 ± 0.6 versus 2.7 ± 1.2, $p < 0.001$). The degree of difference depended on the flow pattern, with the difference becoming greater at higher PI values. To investigate this further, flow patterns were measured in 8 grafts under different levels of filter setting (5, 10, 20, 30, 50 and 100 Hz) in the VeriQ system. Typical changes in the flow pattern occurred under different filter settings: a low filter setting resulted in a smoother flow pattern and increasing the filter setting produced a ‘noisier’ flow pattern with higher PIs. The authors concluded that the Transonic flowmeter displayed a lower PI than the MediStim VeriQ system because of the lower default filter setting (10 Hz versus 20Hz). To ensure consistency, the type of flowmeter and default settings should be described whenever graft flow measurements and derived indexes are provided.

### 4.1.1 Additional supporting evidence

The manufacturer also submitted evidence relevant to the decision problem on predecessor devices of the VeriQ system. Three further studies that were considered relevant were identified by the EAC. These MediStim predecessor devices (CardioMed (CM) and Butterfly Flowmeter (BF) ranges) used the same TTFM principle as the VeriQ system to measure graft flow during CABG. The EAC has reviewed these studies and considers them as relevant

for the assessment of the value of TTFM assessing graft flow with the VeriQ system. A table summarising the 26 relevant studies can be found in appendix E.

Three comparative studies evaluated TTFM against intra-operative fluorescence imaging, and two also used post-operative X-ray angiography. The studies showed variable findings but all authors suggested that TTFM was a comparatively simple technique to use. Balacumaraswami et al. (2005) found good correlation between TTFM and intra-operative fluorescence imaging but suggested that assessing graft patency with TTFM alone might prompt unnecessary graft revision in 10% of cases. Desai et al. (2006) concluded that intra-operative fluorescence imaging is more sensitive than TTFM ($p = 0.023$) for detecting graft errors. Hatada et al. (2011) suggested that measuring the harmonic distortion of the TTFM waveforms was more accurate than intra-operative fluorescence imaging or mean flow and pulsatility index from TTFM.

Five studies indicated that TTFM is a useful tool for predicting early graft failure, but that there is no strong evidence for its ability to predict long-term patient survival. Jokinen et al. (2010) assessed the value of TTFM in terms of predicting short-term graft patency and long-term patient survival (204 grafts) and concluded that TTFM fulfils most of the needs of a good intra-operative tool for quality assessment in CABG procedures. TTFM can predict graft failure within 6 months of the CABG but does not predict long-term outcome. Beran et al. (2010) reviewed the value of TTFM in predicting long-term mortality ($n = 1500$ patients) and considered the measurement of pre-operative left ventricular ejection fraction using echocardiography to be a better independent predictor of a long-term survival than TTFM ($p = 0.004$). Tokuda et al. (2007) carried out an evaluation of TTFM using early post-operative angiographic control (261 grafts) and suggested that TTFM was a useful method for predicting early graft failure. In the follow-up study, Tokuda et al. (2008) showed significant correlation between abnormal TTFM values and mid-term graft failure (104 grafts; lower mean flow [$p<0.001$] and a higher percentage of backward flow [$p < 0.05$]) and suggested that TTFM provides a

good prognostic index for both early and mid-term follow-up. Hermann et al. (2008) also used TTFM to assess the predictive value of measured graft flow on early and medium-term outcomes (985 patients) and found adverse cardiac events to be more prevalent in patients with abnormal flow ($p < 0.0001$). Approximately 1% of patients were shown to have abnormal flow prompting surgical graft revision.

Seven studies (D'Ancona et al. 1999, D'Ancona et al. 2000, Gwozdziewicz et al. 2004, Gwozdziewicz et al. 2006, Leong et al. 2005, Kim et al. 2005, Di Giammarco et al. 2006) used TTFM as a tool for assessing the quality of bypass grafts and in all studies the technique was considered useful for measuring various parameters related to blood flow.

The two studies (Kjaergard et al. 2004, Balacumaraswami et al. 2008) that used TTFM to compare on-pump and off-pump techniques and the three studies (Weber et al. 2009, Norgaard et al. 2009, Takami et al. 2009) in which TTFM was used to compare types of graft showed TTFM to be a useful tool with significant differences in measured values for the various methods and grafts. The single case study (Economopoulos et al. 2010) showed TTFM to be a useful tool for identifying a suspected stenosis. Two of the early studies (Lautensen et al. 1996, Walpoth et al. 1996) showed that TTFM gave flow values that corresponded closely to directly measured blood flow.

In one review Balacumaraswami et al. (2007) concluded that both TTFM and intra-operative fluorescence imaging can reliably detect occluded grafts but cannot consistently detect minor abnormalities. However, TTFM is more likely to under- or overestimate the need for graft revision than intra-operative fluorescence imaging. In another review Mack (2008) similarly suggested that although TTFM provides an objective measurement of graft flow, the technique is more liable to underestimate or overestimate the need for graft revision.

Several of the studies use post-operative X-ray angiography as a comparator because this technique is still considered the 'gold standard' for graft assessment, although it is not the most convenient technique to perform.

TTFM is considered a valuable method of quality control in CABG surgery and it is easier to perform. Routine clinical use of TTFM is recommended by a number of the studies

## *4.2 Summary of economic evidence*

The economic evidence for the VeriQ system comprised a new analysis to assess the cost savings to the NHS of introducing the technology for the assessment of graft flow during CABG surgery.

### 4.2.1 Model structure

The model is constructed to evaluate the cost savings of using the VeriQ compared with clinical assessment to assess graft flow in all patients undergoing CABG. The model considered only the additional costs of using the VeriQ system and not the total costs of the CABG procedure, which are common to both the VeriQ system and clinical assessment. The outcomes considered in the model are complications associated with the CABG surgery. The model is based on a bottom-up approach, evaluating the costs per procedure and applying these to the total population undergoing CABG.

### 4.2.2 Costs and benefits

In the base case, the equipment cost for the VeriQ system was about £100 per procedure and the additional time for measuring flow in three grafts was 2.35 minutes. The equipment costs are based on the VeriQ 2011 (£32,000 with an anticipated life span of 10 years) and an average use of 1.7 probes per procedure (£1582 per PS probe which is valid for 30 uses).

It is assumed that the VeriQ system is used 220 days per year and for 1 patient per day. All time costs in the model are based on the salaries of a CABG team comprised of 6 healthcare professionals (2 cardiothoracic surgeons, 1 anaesthetist, 1 cardiac perfusionist and 2 cardiac nurses). An annual maintenance cost of £1800 per year payable from year 3 to year 10 has not been included in the base-case analysis.

The consequences of using the VeriQ system are based on results from two studies (Kieser et al. 2010, Becit et al. 2007). In the base-case analysis, the

use of the VeriQ system is associated with an increase of 6.58% in the revision rate (a 2.29% increase in minor revisions and a 4.30% increase in major revisions). Costs for the revisions are based on the CABG team time taken to perform the revisions (minor revisions were estimated to cost £11 each and major revisions £180 each).

The outcomes considered are intra-operative issues such as investigation of bleeding, deep sternal infection, and use of an intra-aortic balloon pump and post-operative issues such as peri-operative myocardial infarction and the associated rehabilitation costs. The rates of these outcomes for CABG with and without the VeriQ system are based on Becit et al. (2007). There is no difference in the investigation of bleeding and deep sternal infection. Each intra-aortic balloon pump costs £2657 and the base-case analysis compares a 1% rate for patients with VeriQ and clinical assessment versus a 7% rate for patients with clinical assessment alone. Perioperative myocardial infarction and rehabilitation costs around £1667 and the base case compares a 0% rate for patients with VeriQ and clinical assessment versus a 5% rate for patients with clinical assessment alone. No adverse event costs are included in the model because no adverse events have been associated with use of the VeriQ system.

### 4.2.3 Results

The cost saving in the base case associated with the VeriQ system was £121 per patient based on a VeriQ 2011 (£32,000) with a PS probe (£1582 for 30 uses). However, an annual maintenance cost (£1800) payable from year 3 is not included in the base case. If this cost is included in the analysis the cost saving per patient is reduced to £111.

One-way sensitivity analysis was reported for a number of different parameters, including duration of the measurements, number and cost of probes per procedure, rate and durations of the revisions, cost and rate of complications such as need for intra-aortic balloon pump and myocardial infarction, and the cost of the CABG team. The parameters are described in the assessment report (page 51, table 5).

The results for the sensitivity analysis for the base case can be found in the assessment report (page 57, table 7). The mean number of probes per procedure was varied between1.4 and 2 and this resulted in cost savings of £139 to £103 respectively. When the duration of the TTFM per procedure was varied between 2 and 5 minutes the cost savings varied between £122 and £110. The sensitivity analyses identified the key drivers of the cost saving as the reduction in the use of intra-aortic balloon pump and the rate of perioperative myocardial infarction associated with the use of the VeriQ system. All sensitivity analyses showed a cost saving to the NHS varying between £44 and £330 per patient, apart from the worst case scenario involving the use of intra-aortic balloon pump. The lowest cost saving of £44 per patient was obtained for the worst case scenario for peri- and post-operative myocardial infarction with both arms of the analysis having a rate of 2.5%. The highest cost saving obtained in the sensitivity analyses (£330 per patient) was associated with patients assessed with the VeriQ system having no intra-aortic balloon pumps and those without have a pump use of 14%. The only case in which use of the VeriQ system was not cost saving was an intra-aortic balloon pump use of 3.5% in both arms (that is, use of VeriQ does not reduce use of intra-aortic balloon pump and use of the VeriQ system results in an additional cost of £39 per patient). The EAC has advised that this is an unnecessarily pessimistic view and that the VeriQ system is likely to be cost saving when used appropriately. Thus the sensitivity analysis based on the parameters and ranges identified by the manufacturer has shown that cost savings for the VeriQ system are robust.

The EAC carried out additional analysis to consider the use of the higher specifications of VeriQ and the PQ probe (valid for 50 uses) as well as the PS (valid for 30 uses) probe. The results described in table 6 of the additional analysis undertaken by the EAC show a saving of between £114 and £157 per patient for the six combinations considered (VeriQ 2011, VeriQ 2111, VeriQ 4122 each with PS and PQ probes). Also if annual maintenance costs after 2 years are included in the analysis the saving is between £75 and £118 per patient (table 8 of additional analysis undertaken by the EAC). The EAC also investigated the variations in savings with workload. The base-case

savings for the PS probe (£121) and the PQ probe (£157) assume the device is used 220 days a year. If this is reduced to use only once a week, the savings per patient scanned are £30 for the PS probe and £99 for the PQ probe.

# 5 Ongoing research

The manufacturer and the External Assessment Centre are not aware of any on-going studies using the VeriQ system.

# 6 Authors

Bernice Dillon, Analyst
Mukesh Dhariwal, Analyst
NICE Medical Technologies Evaluation Programme
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