Health Policy Advisory Committee on Technology

Extended Technology Brief

Vagus nerve blocking and gastric artery embolisation for obesity

July 2015
Summary of findings

*Maestro System*

Two randomised controlled trials (RCTs)\(^2\)\(^-\)\(^23\) and one case series\(^24\) were available, all of which were industry sponsored. The two multicentre RCTs were conducted at essentially the same sites in Australia and the USA and the patient inclusion and exclusion criteria were almost identical. In one RCT (n=294),\(^23\) the control group had Maestro devices implanted that generated a very low current; in the other RCT (n=239)\(^2\) no current was generated in the control group devices. In the earlier study,\(^23\) patients in both study arms achieved the same degree of weight loss (16% to 17%). The researchers postulated that the results may have been confounded by the low-level vagal stimulation in the control group causing some beneficial effect.

In the second study,\(^2\) the patients in the Maestro group achieved a greater percentage of excess weight loss (EWL), compared with the control group (24% versus 16%). The researchers noted that the response of patients in the control group was much higher than expected, possibly due to the effect of close monitoring.

The latter study was the pivotal study submitted to the FDA for device approval. Due to the promising nature of the technology and access to 18-month data, the FDA granted device approval, stating that the benefits of the device outweighed the risks. As a condition of approval, the FDA required that the company conduct a five-year post-approval study to collect additional safety and efficacy data in at least 100 patients. An additional, industry-sponsored case series study is underway in Australia,\(^25\) which aims to recruit up to 25 adults with a BMI of 27 to 40 kg/m\(^2\), type 2 diabetes and uncontrolled systolic hypertension; a three-year follow-up is planned. It is not clear whether this study has commenced.

*Gastric artery embolisation:*

The scant published evidence was limited to two small studies: a retrospective, non-randomised comparative study of weight data for patients with upper gastrointestinal bleeding, 19 of whom had left gastric artery (LGA) embolisation and 28 controls who had embolisation of other arteries,\(^8\) and a prospective case series study of five patients.\(^7\) In the comparative study, the LGA group lost more weight at around six weeks (7.3% versus 2% for controls; p=0.006), although the difference was not significant at later follow-up. Safety issues were not discussed. The authors postulated that the procedure could be a therapeutic option for managing obesity. In the prospective study, a mean 16 per cent EWL was recorded at six months. Two very small prospective case series studies are underway in the USA.

It is suggested that both technologies continue to be monitored due to the prevalence of obesity and the need for effective therapies. The Maestro System has been approved in Australia and a small Australian case series may be underway (n=25), although recent
information was not located. Similarly, several small safety studies of gastric artery embolisation are recruiting patients with the aim of receiving FDA approval to conduct a larger safety and efficacy study.

HealthPACT Advice

Due to the current lack of safety and effectiveness evidence supporting the use of these technologies for the treatment of obesity, HealthPACT does not support investment in these technologies in clinical practice at this time. However, HealthPACT recommends that the evidence for these technologies be reviewed again in 24 months.
Two emerging treatments for obesity are discussed in this report: vagus nerve blocking (vBloc® Therapy) using the Maestro® Rechargeable System and gastric artery embolisation.

Maestro® Rechargeable System

The Maestro System blocks the vagus nerve which controls food digestion. The System comprises a small neuro-regulator (similar to a heart pacemaker), a transmit coil and a mobile charger. The neuro-regulator is implanted just under the skin near the ribs and two wires with electrodes are attached to the vagus nerves just above the stomach. The device intermittently blocks vagal nerve signals travelling between the brain and the stomach and pancreas during waking hours. This reduces appetite, stomach expansion and the frequency of stomach contractions as well as the secretion of digestive enzymes, potentially inhibiting calorie absorption. The device is recharged and programmed via radio waves using the external mobile charger and transmit coil, which is placed over the device for short periods of time as required. Maestro System implantation is performed in a hospital as a day procedure and requires laparoscopic surgery and general anaesthesia. The lifespan of the device is 18 months for the neuro-regulator and 36 months for the implanted leads.

Gastric artery embolisation

Gastric artery embolisation blocks blood vessels supplying the upper stomach using biocompatible synthetic beads delivered via an angiographic catheter. The objective is to decrease production of the appetite-inducing hormone, ghrelin, a recently discovered neuropeptide that is predominantly produced by the mucosa of the gastric fundus (upper part of the stomach). In obese patients eating fails to suppress ghrelin secretion. As a result, they do not feel full after eating and tend to overeat. Results from studies on animals and retrospective reviews of patients who underwent gastric artery embolisation for upper gastrointestinal bleeding suggest that this procedure can decrease ghrelin levels and induce weight loss, at least in the short-term.

Company or developer

The Maestro System was developed by EnteroMedics, Inc. (Minnesota, USA).
Gastric artery embolisation does not involve specific proprietary technology aside from the embolisation beads, which are manufactured by various companies.

**Reason for assessment**

Obesity is a major medical issue in many parts of the world, including Australia, and affected people are very difficult to treat successfully. As obesity is a risk factor for heart disease, diabetes and hypertension amongst others, an increase in obesity has been followed by an increase in these comorbidities, which impacts on the capacity of the public health system.

The two approaches outlined in this report are recent attempts to increase the likelihood of successful weight loss in obese people.

**Stage of development in Australia**

- ☒ Yet to emerge (gastric artery embolisation)
- ☐ Established
- ☐ Experimental
- ☐ Established *but* changed indication or modification of technique
- ☒ Investigational (Maestro System)
- ☐ Should be taken out of use
- ☐ Nearly established

**Licensing, reimbursement and other approval**

**Maestro System**

The Maestro System received approval from the Therapeutic Goods Administration as a Class III medical device in late 2011; several months earlier, the technology received the European CE mark. In September 2014, the manufacturer announced that its CE mark had been expanded to the treatment of patients with type 2 diabetes mellitus. The Maestro System received Premarket Approval from the United States Food and Drug Administration (FDA) in January 2015 (the first obesity device to gain FDA approval since 2007) on condition that the company conduct a five-year post-approval study.

**Gastric artery embolisation**

Although surgical procedures do not generally require regulatory approval, an exception is made by the FDA for obesity treatments. With any obesity intervention the FDA has extensive oversight on implementation, including use of a mandated regulatory pathway. A structured process is now in place that allows the investigation of an obesity intervention to move from a small safety and efficacy trial to a larger pivotal trial. To meet this end, an investigational device exemption study (NCT02165124; n=5) of gastric artery embolisation is now recruiting to provide 30-day post-treatment safety data.
Australian Therapeutic Goods Administration approval

☒ Yes (Maestro System)  ARTG number(s):
192883 (regulator); 193393, 193394 (anterior and posterior leads); 193395, 194020, 194021 (transmit coil)

☐ No

☒ Not applicable (gastric artery embolisation)

Technology type
Maestro System: Device
Gastric artery embolisation: Procedure

Technology use
Therapeutic

Patient Indication and Setting

Disease description and associated mortality and morbidity

Overweight and obesity are defined as abnormal or excessive fat accumulation resulting from an imbalance between calories consumed and calories expended. Body mass index (BMI) is based on a person's weight and height and is commonly used to classify overweight and obesity. The World Health Organization defines overweight as a BMI between 25 kg/m$^2$ and 29.9 kg/m$^2$ and obesity as a BMI of at least 30 kg/m$^2$. Globally, the intake of energy-dense foods that are high in fat has increased, while physical activity has decreased due to sedentary work habits, changing modes of transportation and increasing urbanisation.

Common health consequences of overweight and obesity include: cardiovascular diseases (mainly heart disease and stroke); diabetes; musculoskeletal disorders (especially osteoarthritis); and some cancers (endometrial, breast and colon). Additional morbidity can include liver disease, obstructive sleep apnoea, phlebitis (vein inflammation), gout, asthma, depression, polycystic ovarian syndrome and infertility. Disease risk increases as BMI increases. Worldwide, overweight and obesity account for 30 to 40 million deaths each year, 3 to 9 per cent of years of life lost and 3 to 8 per cent of disability-adjusted life-years.

Data from the population-based Australian Diabetes, Obesity and Lifestyle study were used to assess the impact of obesity on health-related quality of life (HRQOL). The study analysed data from surveys conducted in 1999/2000 and 2004/2005 of about 6,000 Australians aged 25 years or older. In this cohort, obesity was associated with a deterioration in HRQOL (assessed with the SF-36 questionnaire) in both the physical and mental health domains over the five-year period. Low HRQOL was also a predictor of weight gain.

Pacific Islanders have a particular problem with obesity, which affects the populations of Australia and New Zealand as these are favoured countries for out-migration (along with the
In the 2011 Australian census, just over 100,000 people reported their country of birth as Fiji, Papua New Guinea or Samoa (other Pacific Island nations were not individually identified); in New Zealand 266,000 Pacific Islanders comprised about 7 per cent of the total population in 2006. The rate of obesity in these populations exceeds 60 per cent.\textsuperscript{17}

An Australian economic analysis based on a survey conducted in 2006 to 2009 of over 240,000 adults aged 45 years or older found that health expenditures for people with a BMI of 30 to 35 kg/m\textsuperscript{2} or more than 35 kg/m\textsuperscript{2} are 19 and 51 per cent higher, respectively, than the costs for people of normal weight.\textsuperscript{18} Significant differences were found for all types of health care including inpatient, emergency department, outpatient and prescription drugs. An estimate of the cost of overweight and obesity to the US medical system was USD 168 billion ($216 billion), more than 16 per cent of all expenditures.\textsuperscript{12}

**Number of patients**

According to the World Health Organization, the worldwide rate of obesity has doubled since 1980. An estimated two billion adults are overweight and over 600 million of these people are obese.\textsuperscript{13} The 2011-12 Bureau of Statistics Australian Health Survey showed that 63 per cent of Australian adults are overweight (35%) or obese (28%); only one-third (36%) of Australian adults have a healthy body weight.\textsuperscript{19} The prevalence of overweight and obesity is higher in men (70%) than in women (56%).\textsuperscript{19} The experience in the USA is similar, with nearly two thirds of American adults being overweight, obese or morbidly obese.\textsuperscript{12} At 28 per cent, the rate of adult obesity in Australia is the fourth highest among the 34 countries in the Organisation for Economic Co-operation and Development (OECD) behind the USA (37%), Mexico (30%) and Hungary (29%).\textsuperscript{19}

**Speciality**

Endocrine, nutritional and metabolic

**Technology setting**

General hospital or specialist hospital

**Impact**

Additive and substitution technology

The surgical technologies described in this report are additive to optimal lifestyle modifications such as healthful eating and adequate exercise.

**Current technology**

Treatments for obesity range from healthy eating and exercise to prescription medicine and surgery. There are several medical devices that can also play a role. The FDA has approved three devices for treating obesity: the LAP-BAND\textsuperscript{®} System (Apollo Endosurgery, Inc., Texas, USA), the REALIZE™ Gastric Band (Ethicon Endo-Surgery, Ohio, USA) and the Maestro Rechargeable System.\textsuperscript{5}
Before medicine is prescribed or surgery is offered, doctors generally recommend lifestyle changes incorporating healthy eating and physical activity. Regardless of treatment modality chosen, patients will need to maintain a healthy lifestyle for the rest of their lives, but even then some patients will not succeed in losing weight or maintaining weight loss.\(^5\)

Unfortunately, regaining lost weight is common after weight loss achieved with lifestyle interventions; studies show that peak weight loss occurs from 6 to 12 months after starting an intervention and that the weight is completely regained within two to five years.\(^20\)

Aggressive therapies, such as bariatric surgery, are typically reserved for obese patients with a BMI over 40 kg/m\(^2\) or a BMI over 35 kg/m\(^2\) and an obesity-related comorbid condition for which more conservative measures have failed. The most common bariatric surgery procedures are Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy and adjustable gastric banding.\(^12\) Unfortunately, surgical interventions are associated with significant morbidity and mortality and some are not reversible.\(^3\) For example, the most commonly reported complications after RYBG include telescoping of the intestine (1%), postoperative anastomotic leak (leakage of intestinal contents; up to 5%); gallstones (up to 36%) and need for further surgery (up to 81%).\(^12\) Alternative safe and effective, minimally invasive and reversible weight-loss procedures are needed.\(^3\)

**Diffusion of technology in Australia**

*Maestro System*

No reports of Maestro System use in Australia were located, despite receiving Therapeutic Goods Administration approval in late 2011. However, a member of the EnteroMedics Board of Directors (2008 to 2011) chaired the largest network of bariatric surgery clinics in Australia (the Australian Institute of Weight Control).\(^21\) The manufacturer issued a press release in 2012 stating that the first commercial shipment of devices had been sent to its Australia distributor, Device Technologies Pty Ltd (NSW, Australia),\(^22\) although this company does not currently list the Maestro System among its products.

*Gastric artery embolisation*

There was no report of this procedure being tested or available in Australia or New Zealand.

**International utilisation**

*Gastric artery embolisation*

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td></td>
<td>check mark</td>
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</table>
**Maestro System**

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
<th>Trials underway or completed</th>
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<tbody>
<tr>
<td>Australia</td>
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<td>Mexico</td>
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<td>Norway</td>
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<tr>
<td>Switzerland</td>
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<tr>
<td>USA</td>
<td>✓</td>
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**Cost infrastructure and economic consequences**

*Maestro System*

A review of the Maestro System reported a cost estimate for the device plus surgery of USD 30,000 to 40,000 ($38,000 to $51,000), not including training costs, and quoted an EnteroMedics, Inc. spokesperson as saying that although the company has not set pricing, it expects costs to be competitive with a gastric band device and gastric bypass surgery (USD 20,000 to 30,000 [$26,000 to $38,000]). The review noted that most payers were unlikely to cover this device unless more definitive efficacy data are reported.³

*Gastric artery embolisation*

Costs for gastric artery embolisation were not located but would be dependent on the degree of overlap with existing embolisation procedures and the need for additional training.

**Ethical, cultural, access or religious considerations**

No cultural, religious or access considerations were identified for either technology.

**Evidence and Policy**

*Maestro System*

**Effectiveness and safety**

Two randomised controlled trials (RCTs) (level II intervention evidence)², ²³ and one case series study (level IV intervention evidence) were identified, ²⁴ (Table 1). All studies were sponsored by EnteroMedics, Inc.
Table 1  Included study characteristics

<table>
<thead>
<tr>
<th>Study / Design</th>
<th>Inclusion criteria</th>
<th>Excluded criteria</th>
<th>Number of patients</th>
<th>Conflicts of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikramuddin et al 20142 “RECHARGE” trial NCT01327976 Australia &amp; USA (10 sites) Prospective RCT (level II intervention evidence)</td>
<td>Age 18 to 65 years; BMI 40 to 45 kg/m² or 35 to 40 kg/m² with ≥1 obesity-related comorbidity, e.g. type 2 diabetes, hypertension or dyslipidaemia; failure to respond to supervised diet/exercise program(s) in the past 5 years</td>
<td>History of bariatric surgery, fundoplication, gastric resection or major upper abdominal surgery; multiple medical condition exclusions; hiatus hernia; smoking cessation in past 6 months; use of diet drugs in past 3 months; overall sustained reduction of more than 10% of body weight in past 12 months</td>
<td>Maestro: 162 (157 received the device) Losses to follow-up at 12 months: 10 Sham device: 77 (75 received the device) Losses to follow-up at 12 months: 9</td>
<td>Study sponsored by EnteroMedics, Inc. Eight of 23 authors had received some form of EnteroMedics, Inc. funding, including two who were company employees.</td>
</tr>
<tr>
<td>Sarr et al 201223 “EMPOWER” trial NCT00521079 Australia &amp; USA (15 sites) Prospective RCT (level II intervention evidence)</td>
<td>As for Ikramuddin et al 2014; failure to respond to supervised diet/exercise program(s) “in which the subject was engaged for at least 6 months”</td>
<td>As for Ikramuddin et al 2014</td>
<td>Active Maestro device: 192 Inactive Maestro device: 102</td>
<td>Study “funded entirely” by EnteroMedics, Inc. Author conflicts of interest were not reported.</td>
</tr>
<tr>
<td>Shikora et al 201324 NCT00555958 Australia, Mexico, Switzerland &amp; Norway (5 sites) Prospective case series study (level IV intervention evidence)</td>
<td>Age 25 to 60 years; type 2 diabetes for ≤12 years with HbA1c levels of 7% to 10% and no significant diabetic complications; BMI 30 to 40 kg/m²; failure to respond to a diet and exercise program</td>
<td>History of gastric resection or major upper abdominal surgery; hiatus hernia; type 1 diabetes; reduction of more than 10% of body weight in past 12 month; medical condition making the patient unfit for general anaesthesia or weight loss; smoking cessation in past 6 months</td>
<td>N = 28 (planned enrolment was 120)</td>
<td>Study sponsored by EnteroMedics, Inc. Ten of 13 authors had received some form of EnteroMedics, Inc. funding, including two who were company employees.</td>
</tr>
</tbody>
</table>

BMI: body mass index; RCT: randomised controlled trial

Ikramuddin et al 20142

This double-blind, sham-controlled RCT (level II intervention evidence) enrolled 239 patients at 10 sites in Australia and the USA between May and December 2011. The recruitment method was not described. Of the 420 people recruited, 181 were rejected for the following reasons: refused to participate; BMI criteria not met; failed the psychiatric evaluation; presence of a medical condition that made the patient unfit for surgery; unable to complete study visits; or hiatus hernia. The included patients had a mean age of 47 years and a mean BMI of 41 kg/m². Statistical analysis of the differences between the patient groups were not provided, although the groups appeared to be similar.

The first year of follow up for this five-year study (estimated completion date December 2016) was reported. The allocation ratio for Maestro to the sham device was 2:1 in permuted block sizes of three or six, stratified by study site and type 2 diabetes status (participants with type 2 diabetes were limited to 10 per cent of enrolment at each site and their randomisation was not stratified by site). The patients, outcome assessors and study sponsor were blinded to treatment allocation, but the surgeons and surgical staff were not,
although their contact with the patients after surgery was limited. Patient inclusion and exclusion criteria are shown in Table 1.

In both groups the devices were implanted under general anaesthesia in a procedure that took 60 to 90 minutes and required five laparoscopic ports. The sham procedure consisted of the same number of skin incisions as for Maestro, but without peritoneal penetration. The sham neuro-regulator did not have electrical leads and dissipated charges within the device. In both groups, the neuro-regulators were programmed to deliver a charge for at least 12 hours per day. All patients attended a weight management program of 17 face-to-face educational sessions on healthful food choices, physical fitness and social support.

The main efficacy outcome was percentage of excess weight loss (EWL), where excess weight is the difference between the patient’s weight at device implantation and the weight required to achieve a BMI of 25 kg/m\(^2\). Based on the results of earlier studies,\(^{23, 24}\) the trial assumptions were that, on average, subjects in the Maestro System group would achieve 25 per cent EWL at 12 months, compared with 5 per cent in the sham group.

**Effectiveness**

The analysis was intent-to-treat. Of the 162 patients in the Maestro group, 157 received the device and 147 (94%) were available for the 12-month follow-up. In the sham group, 75 had the device implanted and 66 (86%) were available for the 12-month follow-up. Most of those without 12-month data withdrew or were lost to follow-up (reasons were not given).

At 12 months:

The mean percentage of excess weight loss (EWL) was 24 per cent in the Maestro group (9% of their initial body weight loss) and 16 per cent (6% of their initial body weight loss) in the sham group (mean difference 9%, 95% confidence interval [CI] 3.1 to 13.9); however, this difference did not meet the primary efficacy objective of a 10 per cent difference between the two groups. In the Maestro group, 52 per cent of participants achieved at least 20 per cent EWL and 38 per cent achieved at least 25 per cent EWL, but this did not meet the primary efficacy objective of at least 55 per cent of participants achieving 20 per cent EWL and 45 per cent achieving 25 per cent EWL.

Although the percentage of EWL in the Maestro device group was less than expected, it was still significantly greater than that achieved by patients in the sham group. The percentage of EWL in the sham group was three times greater than expected, which was attributed to the placebo effect of surgery, daily self-monitoring that was reinforced by interacting with the sham device and participating in the weight management program.

This study was the pivotal trial examined by the FDA when regulatory approval was granted. At that point, an FDA Advisory Committee noted that although the clinical study did not meet its original endpoint, the 18-month data indicated sustained weight loss. Therefore, it
was decided that the benefits of the device outweighed the risks for eligible patients. As a condition of approval, the FDA required that a five-year post-approval study be conducted on at least 100 patients to collect additional safety and efficacy data, including changes in obesity-related conditions and rates of weight loss, surgical revision and device removal.

Safety

Serious adverse events (SAEs) were monitored by an independent data and safety monitoring board. The primary safety objective was an SAE rate related directly to the device, implantation or revision or therapy in the Maestro group of less than 15 per cent. This rate was chosen, in consultation with the FDA, because it was lower than the SAE rate used to support FDA approval of laparoscopic adjustable gastric banding.

SAEs occurred in six of 162 patients (4%, 95% CI 1.4 to 7.9; \( p < 0.001 \)), thus meeting the primary safety objective. The SAEs included:

- neuro-regulator malfunction requiring replacement (n=2);
- pain at the neuro-regulator site requiring device repositioning (n=1);
- complete or partial lung collapse prolonging hospitalisation by two days (n=1);
- gallbladder disease, possibly related to weight loss (n=1); and
- vomiting requiring hiatus hernia repair (n=1).

The site investigator determined the severity and attribution of adverse events that were not deemed to be SAEs. The adverse events with rates higher than 5 per cent are listed in Table 2. A statistical comparison of rates between groups was not provided.

Table 2: The most common adverse events occurring within the first 12 months in Ikramuddin et al 2014²

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Maestro System (N=162) No. of patients (%)</th>
<th>Sham device (N=77) No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at neuroregulator site</td>
<td>61 (38%)</td>
<td>32 (42%)</td>
</tr>
<tr>
<td>Heartburn/dyspepsia</td>
<td>38 (23%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Other pain</td>
<td>37 (23%)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20 (12%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>13 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Belching</td>
<td>13 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Incision pain</td>
<td>12 (7%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>9 (6%)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>
In addition, nine SAEs (6%) were related to the abdominal surgery, including nausea (n=6), intraoperative oozing (n=1), complicated liver biopsy (n=1; this patient was assigned to Maestro but did not receive an implant) and moderate disruption of normal stomach function (n=1). All of these patients required a longer than expected hospital stay (usually an extra day). Combining these SAEs with those related to the Maestro device resulted in an overall rate of 9 per cent (95% CI 4.8 to 14.1) for patients receiving the Maestro device.

Sarr et al 2012

A similar double-blind, sham-controlled RCT (level II intervention evidence) was conducted at 15 sites in Australia and the USA with enrolment starting in 2007. Study sites overlapped with the Ikramuddin et al (2014) study. The study inclusion and exclusion criteria are listed in Table 1. Of the 503 patients assessed for eligibility, 299 were rejected for various reasons. The mean age and BMI of the 294 eligible patients was 46 years and 41 kg/m$^2$. Follow-up was 12 months post-randomisation. The patients and outcome assessors were blinded to treatment allocation.

One to three weeks after implantation of the Maestro device, patients were randomly assigned to either an intervention group (n=192), in which the device was activated for normal functioning, or a control group (n=102) where the device generated impulses at lower amplitudes and frequencies that were assumed to have no clinical effects, based on animal studies. Non-diabetic patients were assigned in a 2:1 ratio and a limited number of patients with type 2 diabetes were allocated in a 1:1 ratio. Patients in the control group were assured that after a one-year period the Maestro device would be fully activated. All patients were encouraged to use the device for 9 to 16 hours daily, and they also received 15 individual counselling sessions on weight management and physical activity.

Effectiveness

As in Ikramuddin et al (2014), the main efficacy outcome was percentage of EWL at 12 months, with the goal being a 10 per cent difference in favour of the active device group. There was no significant difference between groups in percentage of EWL (17% for the active group and 16% for the control group) or the proportion of patients achieving an EWL of at least 25 per cent (22% versus 25%, respectively). Weight loss was linearly related to hours of device use. Quality of life was assessed using three different tools and, although scores improved over the year of treatment, there was no significant difference between the two groups. The authors postulated that their study design may have confounded the results because the vagus nerve may have received small electrical inputs during device safety and impedance checks.

Safety

The primary safety outcome was the rate of SAEs related directly to the device, implantation or revision or therapy. Thirty-five SAEs occurred (23 in the active device group and 12 in the
control group; the number of patients affected was not reported). These were related to: a pre-existing condition (n=17); the operative procedure or anaesthesia (n=4); implantation or revision of the device (n=5); the device (n=4); or other reasons (n=5). Sixteen patients (5%) had the device removed: eight due to an adverse event and eight for personal reasons. A revision procedure was required in 14 patients (5%) for the following reasons: problems with neuro-regulator communication (n=8); pain at the device site (n=3); high impedance in a lead (n=2); and a problem with transmit coil placement (n=1). It was not clear which study arm the patients requiring device removal or revision had been allocated to.

Shikora et al 2013

A small case series study (level IV intervention evidence) enrolled 28 patients at five centres in four countries (Australia, Mexico, Norway and Switzerland). The inclusion and exclusion criteria are listed in Table 1. The patients had a mean age and BMI of 51 years and 37 kg/m², respectively; 69 per cent were women. Maestro Systems were implanted laparoscopically and then activated two weeks later. The devices were activated for 12 to 15 hours daily and patients received 17 individual counselling sessions on weight management.

Effectiveness

The primary 12-month outcomes are shown in Table 3.

Table 3 Effectiveness outcomes at 12 months’ follow-up in Shikora et al 2013

<table>
<thead>
<tr>
<th>Outcome</th>
<th>12 months’ follow-up</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean EWL (N=28)</td>
<td>25%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in mean waist circumference</td>
<td>-11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(N=23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in mean HbA1c (N=28)</td>
<td>-1.0%</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in mean FPG (N=28)</td>
<td>-28%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

EWL: excess weight loss; FPG: fasting plasma glucose

Significant improvements were observed in percentage of EWL, waist circumference and blood levels of HbA1c and fasting blood glucose. The authors noted that the mean EWL of 25 per cent was low relative to conventional bariatric surgeries, but that the safety profile of the Maestro System was more favourable.

Safety

Pain at the neuroregulator site was reported in one patient. The discomfort was eliminated by repositioning the device.
Gastric artery embolisation

Safety and effectiveness

Little published evidence was available for this procedure. The results of a small retrospective, non-randomised comparative study of 19 patients and a prospective case series study of five patients are described below.

Gunn and Oklu 2014

The medical records of 19 patients who had undergone left gastric artery (LGA) embolisation for upper gastrointestinal bleeding between 2000 and 2012 were retrospectively reviewed (level III-2 intervention evidence). Post-procedural weight loss was compared to that of 28 patients who had undergone embolisation of other arteries for upper gastrointestinal bleeding due to various causes. The arteries were embolised using various techniques, including coils, gel foam and polyvinyl alcohol particles. The groups were not significantly different with respect to mean age (62 years) or mean BMI (30.3 kg/m\(^2\) [range 20.3 to 58.9] for the LGA group and 29.2 kg/m\(^2\) [range 18.1 to 50.3] for the control group).

Safety

There was no mention of issues related to safety.

Effectiveness

Two sets of post-procedure weights were available from the medical records. Weight loss was similar for patients with a pre-procedural BMI of at least 30 kg/m\(^2\) and for patients with a BMI of less than 30 kg/m\(^2\) for both patient groups at both time points. There were also no significant differences in degree of weight loss between groups based on the embolisation technology employed.

**Table 4** Post-embolisation weight loss results in Gunn and Oklu 2014

<table>
<thead>
<tr>
<th>Timing of weight measurement (LGA vs control)</th>
<th>Weight decrease for LGA patients (range)</th>
<th>Weight decrease for control patients (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (median 1.3 vs 1.6 months; (p=0.7) )</td>
<td>7.3% (-1 to 17.9)</td>
<td>2% (-18.3 to 13.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Delayed (median 10.4 vs 4.5 months; (p=0.007))</td>
<td>3.5% (-21.1 to 24.3)</td>
<td>0.3% (-17 to 11.5)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

LGA: left gastric artery

Despite the study’s many limitations (retrospective design, patients not being treated for overweight or obesity, small sample size, lack of documentation of ghrelin levels, some
patients not obese and difficulties matching LGA patients with controls), the authors noted that LGA embolisation may be a therapeutic option for obese patients.

With respect to treatment durability, the authors noted that the degree of weight loss was modest and less sustained that seen after bariatric surgery. They postulated that this may be due to the restoration of blood flow in the embolised LGA, the development of collateral blood flow to the fundus or compensatory ghrelin production at other sites in the body.

Kipshidze et al 2013

The “first-in-human” study (level IV intervention evidence) of LGA embolisation and its effect on weight and ghrelin levels was reported in a conference abstract. Five patients with a mean weight of 128 kg (standard deviation [SD] 24) and a mean BMI of 42 kg/m² (SD 7) underwent LGA embolisation. Weight and blood ghrelin levels were measured before and one month after the procedure. Six-month data were reported in a review article.¹⁴

Safety

There were no peri-procedural complications. Three of five patients complained of epigastric discomfort during the first few hours after the procedure, but the results of an endoscopic examination of the stomach and oesophagus were normal.

Efficacy

Weight loss was observed in all patients at one-month follow-up; three- and six-month data were subsequently reported by another author (Table 5).¹⁴

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Weight loss and changes in blood ghrelin levels post-embolisation (N=5)⁷,¹⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time</td>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Baseline</td>
<td>43</td>
</tr>
<tr>
<td>1 month</td>
<td>38</td>
</tr>
<tr>
<td>3 months</td>
<td>37</td>
</tr>
<tr>
<td>6 months</td>
<td>35</td>
</tr>
</tbody>
</table>

Economic evaluation

No economic evaluations were identified for either technology.
Ongoing research

Maestro® System

Three studies are described on ClinicalTrials.gov, all of which are presented in this report. An additional record was located in the Australian New Zealand Clinical Trials Registry on the “RESOLVE” study (ACTRN12613001255774), which is underway at Monash University in Australia (Table 6). The study's status is unclear as the last information was contributed in late 2013. This industry-funded three-year study aims to recruit up to 25 adults with a BMI of 27 to 40 kg/m² who also have type 2 diabetes and hypertension. Follow-up is planned at regular intervals for up to three years after implantation of a Maestro device. No updated information on this study was located.

Gastric artery embolisation

Two small, prospective Phase I studies are underway in the USA (Table 6), both of which aim to enrol five patients and are still recruiting. The studies will use beads to occlude the LGA and its branches.
Table 6  Registered clinical trial characteristics from the Australian New Zealand Clinical Trials Registry and ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patient details</th>
<th>Intervention (no. of patients)</th>
<th>Outcomes</th>
<th>Trial Status (estimated completion date)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maestro System</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Krum et al “RESOLVE”</td>
<td>Prospective case series study</td>
<td>Age 18 to 70 years with BMI 27 to 40 kg/m², HbA1c levels ≥7% and systolic blood pressure &gt;130 mmHg on a stable antihypertensive regimen</td>
<td>Maestro System (N=25)</td>
<td><strong>Primary:</strong> Adverse events, changes in weight, blood HbA1c and fasting blood glucose levels and blood pressure Follow-up at hospital discharge, 1, 7, 14, 30 days; 6 months; and quarterly through 3 years post-implant</td>
<td>Registered in November 2013 but still indicated as “not yet recruiting”</td>
</tr>
<tr>
<td>ACTRN12613001255774</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Sponsored by EnteroMedics, Inc.</td>
<td></td>
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<tr>
<td><strong>Gastric artery embolisation</strong></td>
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</tbody>
</table>
| Syed et al “GET LEAN”  | Prospective case series study   | Age 22 to 65 years with BMI of ≥40 kg/m² (weight <400 pounds owing to imaging table limitations) | Bariatric embolisation using Bead Block® microspheres (Biocompatibles UK Ltd, Farnham, United Kingdom) (N=5) | **Primary:** Adverse events at 12 months  
**Secondary:** Changes in BMI, weight, QOL and appetite hormone levels including ghrelin at 12 months | Recruiting (final data collection September 2015)                                                                 |
| NCT02248688            |                                 |                                                                                 |                                |                                                                          |                                                                                                           |
| Sponsored by Dayton Interventional Radiology |                                |                                                                                 |                                |                                                                          |                                                                                                           |
| **Weiss et al “BEAT Obesity” study** | Prospective case series study | Age18 to 60 years with BMI of 40 to 60 kg/m² (weight <400 pounds owing to imaging table limitations) | Bariatric embolisation using Embosphere® Microspheres (Merit Medical Systems, Inc., Utah, USA) (N=5) | **Primary:** Weight loss at 12 months  
**Secondary:** Adverse events at 30 days; changes in blood pressure, lipid profile, blood ghrelin levels, serum obesity hormones, eating and hunger/satiety assessments, QOL, food intake and gastric motility/emptying at 12 months | Recruiting (final data collection June 2016)  
Note: Elsewhere the authors reported they hope to expand the study to 20 patients with 1-year follow-up, aiming for FDA approval12 |
| NCT02165124            |                                 |                                                                                 |                                |                                                                          |                                                                                                           |
| Sponsored by Johns Hopkins University |                                |                                                                                 |                                |                                                                          |                                                                                                           |

BMI: body mass index; QOL: quality of life
Other issues

Full Sense™ Device

An additional innovative weight loss technology, the Full Sense Device (BFKW LLC, Michigan, USA), was identified for inclusion in this assessment. Full Sense is a temporary and reversible bariatric device that is deployed and removed on an outpatient basis via endoscopy. It has an oesophageal component and a gastric disc connected by a support or strut. Its objective is to induce long lasting satiety by placing pressure on the distal oesophagus and cardia of the stomach.28

The only description of a clinical study in humans is from a 2009 conference abstract.29 The device was endoscopically placed in three patients (mean BMI 44 kg/m^2; mean age 38 years) who achieved an EWL of 28 per cent in 46 days before the device was endoscopically removed as planned. There was no evidence of device migration, ulcers or compromise of the gastrointestinal junction.

A 2013 horizon scanning alert from the National Health Service in the United Kingdom stated that the manufacturer anticipated receiving a CE mark in mid- to late 2014, with a planned limited market release in key bariatric centres in Europe.30 However, very limited information was available on the technology and communication with the manufacturer was not returned. The limited promotional materials noted that the device is not approved for sale in any jurisdiction.28

Training:

The manufacturer has developed a training and certification program (classroom training, observation and supervised implantation) for the Maestro System and guidelines to identify facilities qualified to implement the therapy. Clinicians are trained on device setup and support for both intraoperative and postoperative care, and yearly recertification is required.3

Industry sponsorship and conflicts of interest:

All four Maestro System studies (three published and one planned) were sponsored by the manufacturer, EnteroMedics, Inc. Likewise, of the two studies that reported conflicts of interest for the study authors, most have or had financial ties to EnteroMedics, Inc.

For gastric artery embolisation, aside from the various types of embolisation beads, proprietary products are not involved and the included and ongoing studies are sponsored by universities or, in one case, a radiology group.
Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Maestro System

Total number of studies 3
Total number of Level II studies 2
Total number of Level IV studies 1

Gastric artery embolisation

Total number of studies 2
Total number of Level III-2 studies 1
Total number of Level IV studies 1

Search criteria to be used

“Maestro AND obesity”

“gastric artery embolization AND obesity”

Also employed were ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry, reviews of article bibliographies, manufacturer websites and focused Google searches. Selected references were also provided by HealthPACT

Literature search date

Early April 2015

References


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Vagus nerve blocking and gastric artery embolisation for obesity: July 2015 19