## Technology, Company and Licensing

<table>
<thead>
<tr>
<th>Technology name</th>
<th>ROX Coupler</th>
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<tbody>
<tr>
<td>Technology - Description</td>
<td>The ROX Coupler (ROX Medical, California, USA) is a novel treatment for patients with treatment-resistant hypertension. The device consists of two components: a crossing needle and a stent-like device made of nickel titanium alloy. The ROX coupler acts in a similar manner to a paper clip, joining the femoral artery and vein in the upper thigh via a small channel or anastomosis. Insertion of the ROX Coupler occurs in a cardiac or radiology catheterisation laboratory under local anaesthesia. A spiral target wire is percutaneously inserted into the iliac artery and advanced towards the femoral artery. The target wire marks the site of the vein-artery anastomosis, and a guide wire and crossing needle are then inserted and positioned at the site under fluoroscopic guidance. The crossing needle punctures the femoral vein and artery. The ROX Coupler’s self-expanding stent is positioned at the puncture site, creating a connection between the vein and the artery. A balloon catheter is then used to expand the anastomosis to a diameter of 4 mm. The procedure takes approximately one hour and is fully reversible. (2) The device creates a connection between the external iliac artery and vein, and it has been hypothesised that this will increase arterial compliance whilst reducing systemic arterial pressure in a similar manner as to that observed after the creation of an arterial-venous fistula in end-stage renal disease patients. A measured amount of blood is diverted from the high pressure artery to the low pressure vein at a rate of 800 mL to 1000 mL per minute. The diversion of blood reduces vascular resistance (the force that opposes blood flow through the blood vessels) while increasing arterial compliance (the ability of the vessels to expand and contract with changes in blood pressure), thereby improving systolic and diastolic blood pressure. (1)</td>
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<td>Company or developer</td>
<td>ROX Medical, California, USA</td>
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<tr>
<td>Reason for database entry</td>
<td>At present there is no proven therapy available for patients with treatment-resistant hypertension. These patients are at significant risk of cardiovascular morbidity and mortality.</td>
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<td>Technology - stage in early warning process</td>
<td>Assessment complete</td>
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<tr>
<td>Technology - stage of development</td>
<td>Other</td>
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<tr>
<td>Licensing, reimbursement and other approval</td>
<td>The ROX Coupler is not listed on the ARTG and is considered an investigational device by the United States Food and Drug Administration. The device has received the CE mark and is commercially available in Europe.</td>
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<tr>
<td>Type(s)</td>
<td>Device</td>
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<td>Use(s)</td>
<td>Therapeutic</td>
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Patient Indication and Setting

<table>
<thead>
<tr>
<th>Patient indications</th>
<th>For treatment-resistant hypertension</th>
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<tbody>
<tr>
<td><strong>Disease description and associated mortality and morbidity</strong></td>
<td>Hypertension is defined as abnormally high arterial blood pressure indicated by an adult systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg. Hypertension is a major factor in the progression of cardiovascular disease and is a contributing factor in the rising morbidity and mortality rates associated with coronary heart disease, chronic kidney disease and stroke. Multiple blood pressure measurements should be taken, at least twice, one or more weeks apart, to diagnose hypertension. Lifestyle factors that contribute to an increased risk in the development of hypertension include smoking, moderate to high alcohol intake, a body mass index &gt;25 kg/m², lack of physical activity and a high salt intake. Treatment for patients diagnosed with hypertension would depend on the absolute cardiovascular risk and other concomitant conditions, however modification of lifestyle factors would be advised. Patients not responding to lifestyle modification alone would be candidates for pharmacological options. ACE inhibitors (or angiotensin II receptor antagonists (sartans)), dihydropyridine calcium channel blockers or low-dose thiazide diuretics (for patients aged &gt;65years) may be considered as first-line pharmacological options. Thiazide diuretics should be used with caution as they have been associated with an increased risk of new-onset diabetes. Beta-blockers are no longer recommended as a first-line therapy due to an increased risk of developing diabetes. Monotherapy with antihypertensives is recommended, however combination drug therapy may be required. Treatment-resistant hypertension is defined by the American Heart Association as persistent, elevated blood pressure that remains above blood pressure goals despite the use of three antihypertensive agents. Ideally, one of the antihypertensive agents should be a diuretic (a drug that promotes urine production). A patient whose blood pressure is controlled using four or more medications is also considered to have treatment-resistant hypertension. (3) The long-term prognosis for patients with treatment-resistant hypertension is unknown. Persistent, uncontrolled, elevated blood pressure is a leading risk factor for stroke, myocardial infarction, obstructive sleep apnoea, and heart and kidney failure. Patients with treatment-resistant hypertension are more likely to develop organ damage, such as left ventricular hypertrophy, retinal lesions, kidney disease and heart failure, and atherosclerosis (hardening of the arteries), compared with hypertensive patients who have achieved blood pressure goals.(4) Risk factors for the development of treatment-resistant hypertension include high body mass index, protein in the urine (albuminuria), impaired kidney function, history of cardiovascular disease and black ethnicity.(4)</td>
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The prevalence of treatment-resistant hypertension is difficult to determine. A review of population-based studies within the United States concluded that 9 to 12 per cent of all hypertensive adults meet the American Heart Association’s criteria for treatment-resistant hypertension. This figure decreases to eight per cent when at-home blood pressure measurements are considered. This highlights the impact of the white-coat effect, in which patients exhibit elevated blood pressure in a clinical setting, but not in other settings.(4)

Approximately 4.6 million adults in Australia have hypertension.5 Using the prevalence of treatment-resistant hypertension identified for the United States, it is estimated that 414,000 to 552,000 Australians could be classified as having treatment-resistant hypertension. Within Australia, approximately 47,243 Aboriginal and Torrens Strait Islanders have hypertension.(6) It is therefore estimated 4252 to 5669 Aboriginal and Torrens Strait Islanders may be classified as having treatment-resistant hypertension.

In New Zealand, 1.4 million adults have hypertension.(7) It is therefore estimated 126,000 to 168,000 New Zealand adults may be classified as having treatment-resistant hypertension. However, it is unclear how many patients would be eligible for the ROX Coupler as the inclusion and an exclusion criterion has not been firmly established.

### Technology - specialties
Cardiovascular disease & vascular surgery

### Technology - Setting(s)
General hospital and ambulatory care, Specialist hospital

### Setting - further information

#### Impact

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<th>Alternative and/or complementary technology</th>
<th>Additive or complementary technology</th>
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<td>Current technology</td>
<td>Patients with treatment-resistant hypertension do not respond to conventional medical management. These patients are at significant risk of cardiovascular morbidity and mortality. Two novel devices previously evaluated by HealthPACT are currently being trialled for treatment-resistant hypertension: the Rheos® Baroreflex Hypertension Therapy™ System (CRVx®, Inc., Minnesota, USA) and renal denervation. The Rheos system reduces blood pressure by electrically stimulating the baroreceptors and carotid sinus, which modulates the control of blood pressure by the sympathetic nervous system. Use of the Rheos System is limited due to a lack of follow-up data and the use of inappropriate controls in current clinical trials. Renal denervation removes the sympathetic nerve terminals in the renal arteries by gently heating the inside wall of the artery using radio frequencies emitted by a catheter. This reduces the stimulation of kidney function by the sympathetic nerves, lowering blood pressure. A phase three clinical trial for the leading renal denervation device, the Symplicity™ Renal Denervation System (Medtronic, Inc., Minnesota, USA), failed to meet its primary endpoint of reduced blood pressure at six months.(8)</td>
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<tr>
<th>Health impact</th>
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<tr>
<td>Diffusion</td>
<td>The ROX Coupler is not used in Australia.</td>
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<td>Cost, infrastructure and economic consequences</td>
<td>Insertion of the ROX Coupler is an additional procedure for patients with treatment-resistant hypertension. Increased costs attributable to the procedure include the cost of the device, imaging systems (fluoroscopy) and routine cardiac or radiology catheterisation laboratory costs.</td>
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<tr>
<td>Ethical, social, legal political and cultural impact</td>
<td>No ethical, cultural or religious issues for the ROX Coupler were identified.</td>
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### Evidence and Policy
### Clinical evidence and safety

| For full results and tables please access the full report via the link provided. Safety and effectiveness. Two case series evaluating the ROX Coupler, one prospective and one retrospective were originally included in this brief (level IV interventional evidence). However, since this Brief was finalised an RCT describing the use of the ROX coupler compared to normal medical management was published (level II interventional evidence). For completeness, the results of this study have subsequently been added. The two case series evaluated the safety and efficacy of the ROX Coupler in patients with treatment-resistant hypertension and chronic obstructive pulmonary disease (COPD) (Table 2). Lobo et al 2015 (9) The study conducted by Lobo et al. (2015) is an industry sponsored randomised controlled trial to assess the safety and efficacy of the ROX Coupler. The study’s primary endpoint was mean change in office and ambulatory systolic blood pressure at six months. Secondary endpoints included mean office and ambulatory diastolic blood pressure and any complications attributable to the ROX coupler at six months. One hundred and ninety-five adults with treatment resistant hypertension were screened across 16 centres in Europe for eligibility into the trial. Patients were excluded if they had secondary hypertension (unless it was related to sleep apnoea), renal denervation within six months, chronic kidney disease, type one diabetes mellitus, unstable cardiac disease, or a recent history of heart conditions, severe cerebrovascular disease, a stroke within the previous year, or severe peripheral arterial venous disease. One hundred and twelve patients were subsequently excluded from the trial. Eighty three patients were randomised in a 1:1 ratio via a computer generated process to either the intervention (ROX coupler, n=44) or control (normal medical management, n=39) groups. Six month follow-up data is currently available. Patient details are outlined in Table 3. In general, the included cohorts were middle aged, overweight, stage two hypertensive and were taking between four to five antihypertensive medications. Approximately 20 per cent of patients had prior previous renal denervation. Safety There were no deaths at the six month follow-up. Thirteen procedure-related and twelve device-related adverse events occurred throughout the study period (Table 4). Each patient recovered with no recurrent side effects. There were no adverse events reported in the control group. Efficacy The ROX coupler was successfully implanted in 98% (n=42/43) patients. One patient was excluded at the implantation stage due to unsuitable anatomy. Forty-two and thirty-six patients completed the six-month follow-up in the ROX coupler and control groups respectively. The primary and secondary outcomes of reduced home and office systolic and diastolic blood pressure was achieved in the ROX coupler group but not the control group (Table 5). All patients, however, were still considered hypertensive. Further, it was not reported whether there were differences in blood pressure between the two groups at six months. A sub-analysis of patients, who received renal denervation more than six months prior to the ROX Coupler, had significantly reduced blood pressure at six months compared to control patients (Table 6). Anti-hypertensive medication was reduced in eleven and two patients in the ROX Coupler and control groups respectively (p=0.0303). Four patients in the ROX Coupler group required an increase in the number of anti-hypertensive medications consumed at six months, in contrast to ten in the control group (p=0.0382). Adherence to anti-hypertensive medication throughout the study period was not measured. There were no changes in kidney function in either group at six months. Faul et al 2014 (10) Twenty-four adults with hypertension and COPD were prospectively enrolled into the study. Patients were included if they were between 50 and 80 years of age, had stable COPD of Global Initiative for Obstructive Lung Disease stage II or higher, and had been on the same medication for at least four weeks prior to |
enrolment. Patients were excluded from the trial if they were obese or had a mean pulmonary arterial pressure of more than 35 mm Hg; liver cirrhosis; recent stroke or heart failure (within 6 months); unstable coronary artery disease; peripheral vascular disease; or cancer that might affect their safety. All patients were implanted with the ROX Coupler and received repeat cardiac catheterisation three to six months following the implant. Data from the twelve-month follow-up was provided.

The included cohort were middle aged, had severe to very severe COPD and were hypertensive. Two-thirds of the patients (n=16) had a systolic blood pressure of more than 140 mm Hg at baseline, and five patients had a reading of more than 160 mm Hg. On average the patients were taking two antihypertensive medications. Further demographic information is outlined in Table 7.

Safety

There were no deaths at the 12-month follow-up. There were a number of adverse events, and these were classified as early (those occurring within seven postoperative days) or late (those occurring more than three months after the procedure). Four early adverse events were attributable to the creation of the anastomosis, including a pseudoaneurysm at the femoral access site (n=2), mild chest pressure and chest pain (n=1) and a clot around the shunt (n=1). Late adverse events attributable to the device included: deep venous thrombosis (n=4), closure of the shunt due to lack of clinical improvement (n=1) and venous stenosis of the iliac vein (n=4). All patients were successfully treated.

Efficacy

The median procedure time was 53 minutes (range, 20 to 135 minutes), and was completed without technical difficulty in 20 patients. The types of difficulties encountered while undertaking the procedure on the remaining four patients were not reported.

All patients completed the 12-month follow-up. A sustained reduction in both systolic and diastolic blood pressure was found (Table 8); however, all patients remained hypertensive. Between three and six months the patients exhibited improved oxygen delivery and cardiac output, and lowered systemic and pulmonary vascular resistance. These improvements may have contributed to the reduction in blood pressure (Table 9).

Brouwers et al 2013 (11)

Eight patients, pooled from two-treatment centres in Belgium and Ireland, with treatment-resistant hypertension (taking an average of four anti-hypertensive drugs) and COPD were retrospectively analysed for this case series. All patients underwent creation of an ilio-femoral anastomosis using the ROX Coupler. Patients were followed up for six months postoperatively with appointments at one, three and six months. No inclusion or exclusion criteria were reported.

Safety

No deaths were reported. A lower leg oedema was the only adverse event recorded. There was no information provided regarding treatment for the oedema.

Efficacy

Both at-home and office-based blood pressure measurements exhibited a sustained reduction at six months following the procedure (Table 10). These findings were independent of changes in heart rate and kidney function. The statistical significance of changes in at-home blood pressure recordings was not reported.

A subanalysis of five patients treated at the Belgium centre demonstrated a significant increase in left ventricular function (p<0.05).
### Economic evaluation

The costs associated with treatment-resistant hypertension have not been widely explored in the Australian and New Zealand context. As such, an approximation has been made regarding the yearly cost of antihypertensive medication. The average cost of medication (Table 11) was calculated by determining the most frequently prescribed antihypertensive of each drug class in the 2013-2014 financial year, the number of repeats required for a year and then multiplying by the cost of the medication as listed on the Pharmaceutical Benefits Scheme.

For multi-medication regimes, the most common combination of antihypertensive drugs was determined by the Heart Foundations guidelines. The cumulative cost of medication was produced by adding the most commonly prescribed combination of medication, and accounting for the number of repeats required for a year.

An estimated cost of the medical management required for hypertension within Australia was determined by summing the average cost of maximum price to consumer per year and the cost of four physician consultations, and then multiplying by the range of hypertensive adults in Australia.

It is unclear whether the ROX Coupler will reduce the number of antihypertensive medications required by the patient. As such, the ROX Coupler is an additional expenditure with the cost estimate provided in Table 1.

### Ongoing research

Searches of ClinicalTrials.gov and the Australian and New Zealand Clinical Trials Register identified three clinical trials investigating the ROX Coupler for treatment-resistant hypertension (Table 12). All three trials are being conducted in Europe, predominately in the United Kingdom.

### Ongoing or planned HTA

The ROX Coupler is one of many therapeutic devices currently being marketed to reduce treatment-resistant hypertension. The evidence-base supporting the use of this device is limited, and although the small RCT reported reductions in all blood pressure measurements in the treatment group compared to controls, this trial was not a blinded comparison and did not include a sham arm. Studies have been conducted on a small number of patients and different studies have used different patient inclusion criteria in particular regarding the number of antihypertensive medicines used. The device is not registered by the TGA.

Concerns were also raised regarding the potential for harm with the use of this device, in particular this has been demonstrated in COPD patients. Therefore HealthPACT recommend that no further research on its behalf is necessary at this time, however should normal horizon scanning activity detect TGA approval for the device or the results of the completed RCTs are favourable, further research may be warranted.

### Web link

[EuroScan | Technology | ROX Coupler for treatment-resistant hypertension](#)
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<th>Notes</th>
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| **Other issues**  
The device is also indicated for patients with COPD. Arteriovenous fistulas are routinely created as vascular access points for haemodialysis, and are a similar procedure to creating an ilio-femoral fistula. As such, it can be used to highlight potential complications and risks associated with ROX Coupler in the absence of any high-level evidence. The rate of complication for arteriovenous fistula for vascular access ranges from 16 to 26 per cent with aneurysms, cardiac failure, infection and thrombosis the most frequently encountered complications. Complications are more likely to arise in the elderly and in patients with comorbidities such as diabetes. Further, high-flow arteriovenous fistulas (>2000ml/min) increase the risk of adverse structural and functional cardiac changes, for example, ventricular hypertrophy, left ventricular dilatation, elevated left ventricular diastolic filling pressure and high-output cardiac failure. However, it is presently unclear whether these changes occur only in patients with an underlying cardiomyopathy or in all patients with a high-flow fistula. A study evaluating the ROX Coupler for patients with COPD was excluded from this technical brief; however, it highlights significant issues regarding safety. Fourteen of the fifteen patients enrolled in the study experienced adverse events (93%) attributable to the device. Some patients experienced multiple adverse events (Table 13). Six patients were successfully treated following an adverse event by using conservative methods, while eight patients had their anastomosis closed. One patient died following the last follow-up from right-sided heart failure, and this was likely related to the creation of the anastomosis. There was no difference in the study’s primary outcome (six minute walking distance) or secondary outcome (quality of life), compared with baseline values, at the 12-week follow-up (p>0.05 for both variables). Despite this, surrogate markers of lung and heart function, such as the New York Health Association Class, were improved at the 12-week follow-up (p<0.01). |

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**Notes**: The device is also indicated for patients with COPD. Arteriovenous fistulas are routinely created as vascular access points for haemodialysis, and are a similar procedure to creating an ilio-femoral fistula. As such, it can be used to highlight potential complications and risks associated with ROX Coupler in the absence of any high-level evidence. The rate of complication for arteriovenous fistula for vascular access ranges from 16 to 26 per cent with aneurysms, cardiac failure, infection and thrombosis the most frequently encountered complications. Complications are more likely to arise in the elderly and in patients with comorbidities such as diabetes. Further, high-flow arteriovenous fistulas (>2000ml/min) increase the risk of adverse structural and functional cardiac changes, for example, ventricular hypertrophy, left ventricular dilatation, elevated left ventricular diastolic filling pressure and high-output cardiac failure. However, it is presently unclear whether these changes occur only in patients with an underlying cardiomyopathy or in all patients with a high-flow fistula. A study evaluating the ROX Coupler for patients with COPD was excluded from this technical brief; however, it highlights significant issues regarding safety. Fourteen of the fifteen patients enrolled in the study experienced adverse events (93%) attributable to the device. Some patients experienced multiple adverse events (Table 13). Six patients were successfully treated following an adverse event by using conservative methods, while eight patients had their anastomosis closed. One patient died following the last follow-up from right-sided heart failure, and this was likely related to the creation of the anastomosis. There was no difference in the study’s primary outcome (six minute walking distance) or secondary outcome (quality of life), compared with baseline values, at the 12-week follow-up (p>0.05 for both variables). Despite this, surrogate markers of lung and heart function, such as the New York Health Association Class, were improved at the 12-week follow-up (p<0.01).