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1. Disclaimer and scope

1.1. Products and aliases

This document refers to devices making use of LigaSure™ technology. This technology includes, for laparoscopic procedures, the LigaSure™ 5mm blunt tip device (37 cm and 44 cm), the LigaSure™ Maryland jaw device (37 cm and 44 cm), the LigaSure Advance™ Pistol Grip device, the LigaSure Atlas™ device and the LigaSure™ dolphin tip device. For open surgeries, applicable devices include the LigaSure Precise™ device, the LigaSure Impact™ device, the LigaSure™ small jaw device, the LigaSure™ 5mm blunt tip device (23 cm), the LigaSure™ Maryland jaw device (23 cm), the LigaSure Atlas™ device (20 cm), the LigaSure™ dolphin tip device (20 cm), the LigaSure™ curved jaw device and other reusable LigaSure™-branded instruments. Indications, contraindications, warnings, precautions and procedure steps may vary between products and models, and availability may vary by jurisdiction. Please always refer to indication labelling for your jurisdiction and read all applicable instructions for use provided with the products.

1.2. Data sources

Data regarding preclinical and clinical application of LigaSure™ devices were derived from searches of published literature in PubMed (January 2017) and EMBASE (November 2016). General text searches for LigaSure™ device references were performed in EMBASE to include all published instances of the use of the technology without restriction of time of publication. These results provide an overview of extent of usage of the technology.

For clinical evidence data of LigaSure™ technology usage, structured searches were performed using PubMed for peer-reviewed literature applying consistent exclusion criteria across searches for specific surgical indications (see Section 5, Structured literature search details). Results were restricted to publications based on data obtained within the most recent 10 years of the search (2007 and onwards), and excluded editorials/commentaries, articles with no abstract, those that did not report relevant clinical data (such as animal or ex vivo studies), those that reported data on fewer than 20 patients, those which were not focused on outcomes related to the technology (that is, no mention of vessel sealing or hemostasis), and articles which did not reference LigaSure™ devices or generic LigaSure™ technology (electrosurgical or radiofrequency bipolar vessel sealing).

1.3. Analysis

Clinical results from individual studies are presented as reported (including indication of statistical significance where determined). Where data are amalgamated from multiple reports, please note that the individual studies will vary in terms of design, protocol, surgical technique and patient population, which may limit conclusions drawn from direct comparison and relevant analysis of statistical significance. The resulting figures, however, provide insight into clinical outcomes that have been achieved using LigaSure™ devices in vessel sealing during surgical procedures.
2. Introduction to LigaSure™ technology

2.1. Overview

<table>
<thead>
<tr>
<th>Summary and key messages</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ <strong>Answers unmet surgical need:</strong> Blood loss is still a major concern during surgical procedures and LigaSure™ technology enables efficient, electrosurgical division and sealing of tissues where the control of blood loss is required.</td>
</tr>
<tr>
<td>▪ <strong>History of development:</strong> LigaSure™ devices span almost 20 years of continuous development and improvement to meet current healthcare needs.</td>
</tr>
<tr>
<td>▪ <strong>Extensive worldwide usage:</strong> LigaSure™ technology has over 1,300 published reports of its use in a broad range of surgical procedures spanning 63 countries around the world.</td>
</tr>
<tr>
<td>▪ <strong>Excellent preclinical performance data:</strong> LigaSure™ devices have been tested in pre-clinical animal and ex vivo human tissue models, demonstrating sealing times of 10 seconds or faster with the LVS generator, or 2-4 seconds with the ForceTriad™ energy platform. The applicator provides seal quality resistant to supraphysiological burst pressures for vessels ranging from small (2-3 mm) to large (up to and including 7 mm).</td>
</tr>
</tbody>
</table>

2.2. Prelude

LigaSure™ technology is used in surgical procedures to divide and seal vessels up to and including 7 mm in diameter. The devices are electrosurgical in nature, using current delivered to patient tissues to effect tissue sealing. The complete LigaSure™ vessel sealing system comprises the vessel sealing device (the LigaSure™ sealer/divider), and the energy platform (such as the ForceTriad™ energy platform, the Valleylab™ LS10 generator or the Valleylab™ FT10 energy platform). The vessel sealing device delivers a combination of pressure and electrical current to tissues, the current is provided in a smart algorithm by the energy platform, using tissue-sensing technology (TissueFect™) to control energy delivery. The technology is suitable for use wherever the division and ligation of vessels is desired during general open or minimally invasive surgical procedures. This document presents background information and associated dossiers provide clinical evidence demonstrating the application of LigaSure™ technology in improving surgical procedures and patient outcomes.

2.3. The surgical application: Hemostasis

In surgery, for the patient’s health, as well as to ensure maintenance of adequate visualization, the operative field must stay free of excess blood and other fluids. This is accomplished by hemostatic techniques, whereby dissection is only carried out in blood-vessel-free planes, and when necessary, hemostatic devices are used.

2.3.1. Various methods of controlling blood loss

Methods for controlling bleeding during surgery vary in terms of the immediacy and desired length of action of their effect. A general, non-comprehensive overview of some hemostatic methods is shown in Figure 2-1. The more durable means of preventing excessive blood loss include making use of intrinsic components from the patient’s own tissues, from providing a matrix to support the natural clotting process, to electrosurgical techniques which alter the vessel collagen to collapse or fuse the vessel lumen to create a permanent seal. In the case of some electrosurgical instruments, tissue/vessel division is performed simultaneously to ligation, thereby preventing blood loss from the separated vessel.
Figure 2-1 Methods of surgical hemostasis

Immediate

- Mechanical Extrinsic
  - Gauze/Pads

- Chemical
  - Glue/Cyanoacrylates

Permanent

- Mechanical Intrinsic
  - Electrosurgical
  - Ultrasonic
  - Laser

- Mechanical Extrinsic
  - Sutures
  - Clips
  - Staples

- Biological
  - Cellulose
  - Collagen
  - Gelatin

- Chemical
  - Thrombin
  - Activator

- Mechanical Intrinsic
  - Thrombin Activator

Shown are several options (a non-comprehensive list) for hemostasis that can be intraoperatively deployed. Placement along the timeline indicates a typical expected duration of effect, assuming no failure. The intrinsic methods make use of body components, such as the natural clotting process captured in the matrix of the biological agents indicated, or the fusion of tissues/structures for the mechanical. Extrinsic methods rely on external structures to provide the seal, which may be subsequently removed (such as pads) or may be absorbed (as in the case of some biologics). Adapted from references 13,14.

2.3.2. Electrosurgery

As mentioned (section 2.3.1), electrosurgery is one method of hemostasis. These technologies create an electrical current through the patient to generate localized bursts of heat to coagulate tissue. The electricity oscillates at radiofrequencies (hence sometimes referenced as radiofrequency or RF electrocoagulation), which are well above frequencies for normal nerve function, preventing devices from triggering muscle stimulation.

The waveform of energy delivery determines the function of the device:

- Cut mode: dissects tissue and uses a low voltage with a long duty cycle
- Coagulation mode: cauterizes tissue using a higher voltage with a shorter duty cycle
- Blend mode: uses intermediate voltage and duty cycle length to achieve both dissection and coagulation of the tissues simultaneously with dissection.

The energy from these waveforms is delivered to patient tissues via:

- Monopolar delivery: the electric circuit passes from the generator through the patient, and back to the source via a separately positioned return electrode (Figure 2-2A)
- Bipolar delivery: the electric circuit passes only through tissue positioned between graspers of the device, obviating potential issues of return electrode misplacement or detachment (Figure 2-2B)
Monopolar and bipolar forms of electrosurgery differ in the paths taken by the current. In the schematic on the left (A) monopolar electrosurgery with monitoring of the return electrode is shown. Current follows along the magenta arrows from the source (lower left) and through the patient, returning via the patient return electrode (PRE, blue rectangle). The layout shown here includes a monitoring system for the bisected PRE pads (black arrows) to ensure proper contact minimizing risk of patient injury. In contrast, for bipolar surgery (B), the current passes only through tissue grasped between the forceps, reducing risks to the patient, including from misplaced or detached PREs.

2.4. LigaSure™ technology

LigaSure™ technology is based on bipolar electrosurgery, commonly referenced as electrothermal bipolar vessel sealing (EBVS). The complete system for the sealing of vessels during surgery (previously known as the LigaSure™ Vessel Sealing System, or LVSS) comprises the bipolar device, the energy platform (including the ForceTriad™ energy platform, the Valleylab™ LS10 generator, or the Valleylab™ FT10 energy platform), and the TissueFect™ sensing system, which, using data from the applicator device analyzed at 3,333 to 434,000 data points per second (dependent on the generator), senses the properties of the tissue being grasped to optimize vessel-sealing performance⁴. The LS10 generator and the ForceTriad™ and FT10 energy platforms include the TissueFect™ technology. The sealing occurs through the application of a potential difference between the electrodes of the grasping device, which denatures collagen and elastin within the vessel wall and surrounding connective tissue. The addition of extreme pressure applied by the instrument causes the denatured and reformed collagen and elastin in the tissue bundle or blood vessel to form a hemostatic plug or seal. As a method engaged for hemostasis (section 2.3.1), use of the system is intended to provide an alternative to clips or suture for permanent vessel closure during and after surgery.

2.4.1. Energy platform

The current required for the tissue dividing and vessel sealing functions of LigaSure™ devices is provided by generators designed to provide multiple waveforms for any type of electrosurgery. LigaSure™ device-compatible systems include the ForceTriad™ energy platform and the newer generation Valleylab™ LS10 generator and Valleylab™ FT10 energy platform. These devices (ForceTriad™ and FT10 energy platforms) provide modes to deliver monopolar, bipolar, and LigaSure™-specific waveforms (the LS10 generator provides only the LigaSure™ waveform). In its contact with tissue, the LigaSure™ device provides energy

delivery and acts as a sensor. The device provides data to the energy delivery platform and is subjected to feedback regulation via the TissueFect™ system. The system provides data to the instrument regarding the resulting effects on the tissue. In LigaSure™ mode, the system can be set to automatically complete the sealing, registering an auditory signal when the cycle is complete. A preclinical comparison of a LigaSure™ device as part of the older generation LVSS and the same device with the ForceTriad™ energy platform in blood vessels of various type and size from a porcine model found the use of the ForceTriad™ energy platform to be associated with statistically significantly shorter sealing times (p < 0.05) and higher burst pressures (p < 0.01), although for both power sources, the LigaSure™ device achieved supraphysiological burst strengths. The latest version of the power generator, the FT10 energy platform, demonstrates still further improvements on the ForceTriad™ energy platform.

2.4.2. Preclinical and laboratory data

To minimize patient risk, and to enable analysis of parameters that would not be possible in the live patient, experimental studies to assess instrument performance have been performed. These consist of animal studies (mostly porcine) of various types of vessels, and ex vivo human tissue, immediately after tissue removal or post-fixation. Details of studies can be found in Table 4-1.

2.4.2.1. Burst pressure

A key parameter not readily measurable in vivo in patients is the pressure to which newly divided and sealed vessels can be subjected before seal failure, or the burst pressure Figure 2-3. Across numerous analyses, in vessels extracted from human patients peroperatively (mesenteric vessels) and in animal studies of vessels (porcine, bovine and ovine), LigaSure™ devices have achieved burst pressures well above normal physiological pressures. Figure 2-3  LigaSure™ device supraphysiological burst pressure measurements

Data are compiled from comparable studies in animal and human tissue removed during surgery (mesenteric vessels) and examined ex vivo. Animal data for small vessels are all from porcine models, while animal large vessel data consist of porcine, bovine and ovine. Bars represent weighted means across studies of the ratio of the mean reported burst pressure as a multiple of physiological pressure (taken as 250 mm for blood vessels), N is shown for the total number of individual measurements, and error is indicated as standard error of the mean (SEM).
2.4.2.2. Sealing Time

In addition to the security of the created seal, the average time for the device to complete the sealing cycle is another operative parameter for a user to consider. The latter is in part dependent on the power generator used, where across different sizes of vessels tested in animal models from 2-7 mm, shorter sealing times have been observed using the ForceTriad™ energy platform\textsuperscript{10,11} with LigaSure™ devices in comparison to the original LigaSure™ Vessel Sealing System Generator\textsuperscript{6,10-12,16} (Figure 2-4). Direct comparisons in the same study of the ForceTriad™ energy platform and the earlier version generator, statistically significantly shorter (p < 0.05) seal times were observed. Even given the performance improvement observed with the ForceTriad™ energy platform over the original generator, the newer version FT10 demonstrates still further reductions in seal time over the ForceTriad™ energy platform, illustrating the continued improvement in performance in the LigaSure™ technology energy platform\textsuperscript{b}.

Figure 2-4 Vessel sealing times in experimental models

![Graph showing sealing time comparison between LVSGen and ForceTriad](image)

Although multiple factors will influence the vessel seal time, the power generator used can also have a significant impact on the time to complete the vessel seal using LigaSure™ devices. In animal models, the ForceTriad™ energy platform\textsuperscript{10,11} has demonstrated shorter sealing times than with the original version LigaSure™ Vessel Sealing System generator (LVSGen)\textsuperscript{6,10-12,16} (p<0.001, two-tailed t-test), although both have mean times under 10 seconds. Data aggregated from animal studies (LVSGen: porcine\textsuperscript{6,9-11}, ovine\textsuperscript{16} and bovine\textsuperscript{12}; ForceTriad™, porcine\textsuperscript{10,11}) only where the generator used was described. In direct head-to-head comparisons of the LVSGen and ForceTriad™ in porcine vessels of various sizes, a significant reduction in seal time was also observed\textsuperscript{10,11} (p < 0.05). Total counts of individual measurements are indicated on the bars, and error bars is represented by standard error of the mean (SEM).

2.4.2.3. Thermal damage

A further consideration for use of LigaSure™ devices in clinical applications is the extent of thermal changes caused by the device to assess the potential for unintended damage that may occur in patient tissues. In the preclinical setting, the temperatures generated by the grasping jaws of the LigaSure™ device and the extent of tissue necrosis have been measured. At the point of sealing, mean maximum temperatures ($T_{\text{max}}$) of the instrument (measured by thermal camera imaging of the jaw surface at $85 \pm 3\,\text{°C}$) and of the cutting blade ($103.1\,\text{°C}$) have been measured in porcine models, while 2 mm from the device, a mean $T_{\text{max}}$ of $55.5 \pm 2.4\,\text{°C}$ has been determined in bovine tissue.\textsuperscript{12} Separately from temperatures, histological examination of tissue samples have been used to measure the range of effect (Figure 2-5) in human (mesenteric vessels from intestine\textsuperscript{7}) and animal models (porcine carotid artery segments\textsuperscript{6} and multiple vessel types\textsuperscript{9}). The weighted mean distance of tissue changes from the sealing point across these studies is $2.9 \pm 0.3\,\text{mm}$.

2.4.3. A history of innovation

Since the introduction of the first LigaSure™ device in 1998, continual development has seen the release of multiple devices employing LigaSure™ technology for open and laparoscopic electrosurgical applications, spanning a wide array of indicated surgeries (Figure 2-6).

2.4.4. Surgical indications

The LigaSure™ vessel sealing system (including the devices and energy delivery) is designed for use in minimally invasive (laparoscopic) or open procedures where ligation and division of vessels, tissue bundles, and lymphatics is desired. Note that different devices have different specific surgical indications and these should always be confirmed in the instructions for use accompanying the device according to the local jurisdiction.
2.5. Extensive worldwide usage

Publications referencing LigaSure™ devices demonstrating good performance in surgical settings originate from a wide range of countries (Figure 2-7). LigaSure™ technology was also included among medical supplies (“ligasure vessel sealing equipment, a steam sterilizer, obstetric labor table and intensive care ward beds”) provided by the World Health Organization to a camp in Damascus, Syrian Arab Republic in 2013 as part its health response to the ongoing situation6. Overall, there is published evidence of LigaSure™ use in:


Figure 2-7 LigaSure™ devices have been applied in clinical settings globally

Highlighted are countries of origin for publications demonstrating the successful use of LigaSure™ technology in clinical settings across all surgeries for which the devices have been indicated.

2.6. Dossiers regarding LigaSure™ devices in procedures

In this series of documents, use of LigaSure™ devices in hysterectomy, colectomy, hemorrhoidectomy, and thyroidectomy is discussed.

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3. Key messages for LigaSure™ devices in clinical applications

LigaSure™ technology has also demonstrated excellent outcomes for patients in clinical settings. Key, common findings from analyses across hysterectomy, colorectal procedures (colectomy and hemorrhoidectomy), and thyroidectomy are indicated below (Table 3-1). Individual dossiers for each surgery are available for further details.

Table 3-1  General LigaSure™ technology outcomes across four indications (colectomy, hemorrhoidectomy, hysterectomy, and thyroidectomy)

<table>
<thead>
<tr>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extensive worldwide usage:</strong> LigaSure™ technology has over 1,300 published reports of its use in a broad range of surgical procedures spanning 63 countries around the world. (^{G1-G251})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compared with conventional ligation:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreased operative time compared with conventional ligation:</strong> Across studies reporting operating time (total 32 in 10-year search window for the four procedures), LigaSure™ devices have on average reduced procedure time by 23.1% (±3.1% SEM) compared to conventional ligation. (^{17-48}) Time differences (difference in mean times within these studies) have ranged from equivalency (open hemorrhoidectomy) (^{38}) to time reductions of 106 min (of 349 min radical hysterectomy procedure). (^{52})</td>
</tr>
</tbody>
</table>

| Reduced intraoperative blood loss compared with conventional ligation: Across studies reporting volumetric blood loss (total 17 in 10-year search window for the four procedures), the use of LigaSure™ devices has reduced these losses by an average of 34.6\% (±5.6\% SEM) compared to conventional ligation. \(^{17,19,23-25,28-34,36,41,42,44,46}\) Reductions (difference in mean blood loss within these studies) have ranged from 1 ml (of 1.3 ml in open hemorrhoidectomy) \(^{44}\) to 416 ml (of 999 ml in radical abdominal hysterectomy). \(^{32}\) |

| Rates of operative complications are similar or reduced with LigaSure™ technology: LigaSure™ devices have reduced or had equivalent risks of complications compared to conventional ligation in several procedures. These include statistically significant reductions in infections after hysterectomy, \(^{37}\) and transient hypocalcemia \(^{49}\) and hypoparathyroidism \(^{51}\) after thyroidectomy. In the treatment of hemorrhoid disease, LigaSure™ devices have achieved significant reductions in the risk of recurrence (compared to stapled hemorrhoidopexy \(^{50,51}\)) and overall post-operative complications (compared to open \(^{50}\) and closed \(^{50}\)). |

| Potential to reduce costs due to complications: Interventions and additional operating room usage required to treat complications can considerably increase costs. \(^{34,52}\) Improvement of patient safety endpoints with LigaSure™ devices in comparison to conventional ligation, would potentially decrease complication-related cost burdens where the use of LigaSure™ technology resulted in significant \(^{31,37,48,49}\) and non-significant \(^{37,47,48}\) reductions in various post-operative complications. |

| Substantial cost savings reported with LigaSure™ devices: In comparison to suture ligation, LigaSure™ devices have been reported to reduce hospital, \(^{14}\) staffing, \(^{34}\) and per-procedure costs. \(^{17,46,53,54}\) |

\(^{d}\) Always refer to product labeling for indications for use of the associated LigaSure™ device (see section 1.1.)

\(^{e}\) SEM, standard error of the mean. Source data used in calculation available on request. \(^{46}\).
Compared with other energy devices:

- **Faster or equivalent operative time compared to other energy devices**: In comparison to other energy devices, LigaSure™ technology has shown similar\textsuperscript{55,56} and significantly reduced operative time for monopolar scissors\textsuperscript{46,57} and ultrasonic technology.\textsuperscript{58-60}

- **Reduced or equivalent intraoperative blood loss**: Compared to other energy devices, LigaSure™ technology has achieved similar\textsuperscript{55,56,59,60} and significantly lower blood loss.\textsuperscript{58}

- **Equivalent complication rates**: There have been no increased risks of complications with LigaSure™ technology compared to other energy-based methods of hemostasis.\textsuperscript{45,46,49,50,57,60-64}

- **Lowers the cost of care**: Substantial savings with LigaSure™ technology have been achieved when compared to reusable monopolar scissors,\textsuperscript{57,65} even when specifically including costs of disposal of the single use device\textsuperscript{65} and compared to ultrasonic technology device costs.\textsuperscript{53,54,64,66,67}
4. Source data tables
Refer to section 1.2 for scope of literature presented in the following data tables.

4.1. Data table summary: LigaSure™ technology preclinical data

<table>
<thead>
<tr>
<th>Source</th>
<th>Model</th>
<th>Device</th>
<th>Generator</th>
<th>Measure</th>
<th>Detail</th>
<th>N</th>
<th>Value</th>
<th>Error</th>
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</thead>
<tbody>
<tr>
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<td>porcine</td>
<td>LS Blunt tip</td>
<td>NR</td>
<td>BP</td>
<td>5-7mm</td>
<td>66</td>
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<td></td>
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<td>Sticking</td>
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<td>836</td>
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<td>591</td>
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<td>NR</td>
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<td>TS (degC), thermosensor</td>
<td>max T</td>
<td>8</td>
<td>86</td>
<td>NR</td>
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<td>85</td>
<td>NR</td>
</tr>
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<td>LS Atlas</td>
<td>LVSGen</td>
<td>BP</td>
<td>5.35mm</td>
<td>40</td>
<td>484</td>
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<td></td>
<td>SF</td>
<td>5.35mm</td>
<td>40</td>
<td>0.091</td>
<td>NA</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Time (s)</td>
<td>5.35mm</td>
<td>40</td>
<td>9.1</td>
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</tr>
<tr>
<td>Mantke R, et al., 2011⁶</td>
<td>porcine</td>
<td>LS Dolphin</td>
<td>LVSGen</td>
<td>BP</td>
<td>&lt;5mm</td>
<td>37</td>
<td>965</td>
<td>364</td>
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<td></td>
<td></td>
<td>Time (s)</td>
<td>&lt;5mm</td>
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<td>11.7</td>
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<td></td>
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<td>TS (mm)</td>
<td>depth</td>
<td>37</td>
<td>2.5</td>
<td>0.59</td>
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<td>Model</td>
<td>Device</td>
<td>Generator</td>
<td>Measure</td>
<td>Detail</td>
<td>N</td>
<td>Value</td>
<td>Error</td>
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<td>-------------------------</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>veins</td>
<td>30</td>
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<td>NR</td>
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<td>TS (mm) depth</td>
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<td>3.37</td>
<td>1.44</td>
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<td>NR</td>
<td>NR</td>
<td>BP</td>
<td>NR</td>
<td>24</td>
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<td>Katsuno G, et al., 2010</td>
<td>porcine</td>
<td>LS Atlas</td>
<td>ForceTriad™</td>
<td>Time (s)</td>
<td>3.8mm</td>
<td>20</td>
<td>3.5</td>
<td>0.7</td>
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<td>LVSGen</td>
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<td>Tsunezuka Y, et al., 2010</td>
<td>human lung</td>
<td>LS V</td>
<td>NR</td>
<td>BP</td>
<td>thick PA (&gt;5mm)</td>
<td>12</td>
<td>399</td>
<td>147</td>
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<td></td>
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<td>thin PA (&lt;5mm)</td>
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<td>BP</td>
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<td>999.43</td>
<td>NR</td>
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<td>884.67</td>
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<td>NR</td>
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<td>ForceTriad™</td>
<td>Device failure (%)</td>
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<td></td>
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<td>2-3mm</td>
<td>13</td>
<td>0</td>
<td>NR</td>
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<tr>
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<td>4-5mm</td>
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<td>0</td>
<td>NR</td>
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<td>6-7mm</td>
<td>13</td>
<td>0</td>
<td>NR</td>
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<td>Time (s)</td>
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<td>2.85</td>
<td>1.54</td>
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<td>3.54</td>
<td>2.62</td>
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<td>Lamberton GR, et al., 2008</td>
<td>bovine</td>
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<td>BP</td>
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<td>744.43</td>
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<td>4-5mm</td>
<td>13</td>
<td>1261.45</td>
<td>NR</td>
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<td>645.16</td>
<td>NR</td>
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<td>LVSGen</td>
<td>Device failure (%)</td>
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<td>6-7mm</td>
<td>13</td>
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<td>NR</td>
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<td>Time (s)</td>
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<td>1.56</td>
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<td>7.2</td>
<td>2.38</td>
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<td>6-7mm</td>
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<td>6.77</td>
<td>2.62</td>
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<td>TS (degC)</td>
<td>10</td>
<td>55.5</td>
<td>2.4</td>
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<td>Source</td>
<td>Model</td>
<td>Device</td>
<td>Generator</td>
<td>Measure</td>
<td>Detail</td>
<td>N</td>
<td>Value</td>
<td>Error</td>
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</tr>
<tr>
<td>Hruby GW, et al., 2007&lt;sup&gt;a&lt;/sup&gt;</td>
<td>porcine</td>
<td>LS V</td>
<td>LVSGen</td>
<td>BP</td>
<td>&lt; 3mm</td>
<td>73</td>
<td>569.4</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BP</td>
<td>3-5mm</td>
<td>38</td>
<td>557.8</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BP</td>
<td>5-7mm</td>
<td>3</td>
<td>533.7</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (s)</td>
<td>&lt; 3mm</td>
<td>73</td>
<td>4.1</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (s)</td>
<td>3-5mm</td>
<td>38</td>
<td>5.7</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (s)</td>
<td>5-7mm</td>
<td>3</td>
<td>8</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TS (degC)</td>
<td>max T</td>
<td>10</td>
<td>103.14</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TS (mm)</td>
<td>depth</td>
<td>2</td>
<td>4.5 (arterial)</td>
<td>NR</td>
</tr>
</tbody>
</table>

degC, degrees Celsius; NR, not reported; LVSGen, LigaSure™ vessel sealing system generator; PA, pulmonary artery; s, seconds. Measures: BP, burst pressure; SF, seal failure rate; Sticking, tissue sticking rate; Time, cycle completion time seconds; TS, thermal spread.
5. Structured literature search details

5.1. Searches performed

Structured searches were performed to identify literature reporting on clinical applications of LigaSure™ technology. The searches were divided into two streams: one to identify the most recent clinical evidence of the use of LigaSure™ devices (within the last 10 years), and a second parallel search to identify all clinical applications of LigaSure™ technology, regardless of time, to identify settings in which the devices have been used in patient care. The searches for hysterectomy and colorectal procedures were performed on February 27, 2017. Specifically, for thyroid surgery, the search was composed to capture any reference to LigaSure™ technology. On full text screening, only those publications were retained that applied to the LigaSure™ small jaw device. The PubMed search for peer-reviewed clinical evidence in thyroidectomy was performed on March 17, 2017.

Table 5-1: Structured searched in PubMed to identify relevant LigaSure™ technology data

<table>
<thead>
<tr>
<th>Index</th>
<th>Aim</th>
<th>Search string</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>LigaSure™ by product name</td>
<td>ligasure*[tiab] OR ligasuretm*[tiab] OR ligasurev*[tiab]</td>
<td>614</td>
</tr>
<tr>
<td>#3</td>
<td>Publication years of interest</td>
<td>&quot;2007/01/01&quot;[PDat]:&quot;2018/12/31&quot;[PDat]</td>
<td>9,418,446</td>
</tr>
<tr>
<td>#5</td>
<td>Non-clinical data</td>
<td>&quot;ex vivo&quot;[tiab] OR cadaver*[tiab] OR &quot;deceased donor&quot;[tiab]</td>
<td>78,271</td>
</tr>
<tr>
<td>#6</td>
<td>Animal data</td>
<td>Search terms for animal studies^69</td>
<td>6,291,401</td>
</tr>
<tr>
<td>#7</td>
<td>LigaSure™ (by name or generic), restricted to publication years, excluding animal, non-clinical, and non-primary data</td>
<td>(#1 OR #2) AND #3 NOT (#4 OR #5 OR #6)</td>
<td>3,656</td>
</tr>
<tr>
<td>#8</td>
<td>All hysterectomy procedures</td>
<td>(hysterectomy*[tiab] OR hysterectomy*[MeSH] OR &quot;hysterectomy,vaginal&quot;<em>[MeSH]) AND (surgery</em>[tiab] OR &quot;surgical procedure&quot;<em>[tiab] OR &quot;General Surgery&quot;</em>[MeSH] OR &quot;Surgical Procedures, Operative&quot;*[MeSH])</td>
<td>34,056</td>
</tr>
</tbody>
</table>
The original searches designed above revealed few relevant comparative studies reporting on LigaSure™ device usage in colectomy, although broader searches indicated wider use of the technology. For colectomy surgeries only then, the above searches were supplemented with hand searches, manual screening of article contents (to confirm usage of a LigaSure™ device when not otherwise mentioned in the abstract) and the inclusion of publications after 2007, which may also have referenced pre-2007 data.

The second search, to reveal all clinical instances of LigaSure™ device use, including incidental mentions of use of the technology even if not the focus of the study, was performed using EMBASE. This database includes coverage of non-PubMed-indexed journals and congress reports to thus provide a comprehensive survey of LigaSure™ device use (Table 5-2). A differential search was performed May 2017 to retrieve new records from 2017 and updated or added from 2016, yielding 166 publications to screen for additional settings where LigaSure™ technology has been used.

Results from the various searches were exported from their respective databases as search strings (PubMed) and .RIS files (EMBASE) for integration into the Sourcerer software utility for literature screening and review. Duplicate articles returned from the different sources were automatically removed.
5.2. Screening literature results

5.2.1. Screening general search (EMBASE) results

The purpose of the EMBASE search as described (Section 5.1) was to capture as many references (by name) of LigaSure™ device use in both peer-reviewed and non-peer-reviewed literature. As such, the results were not screened for exclusion criteria, but for surgery type and geographical location to verify clinical application of the technology.

5.2.2. Screening returned results for evidence (PubMed)

The articles returned from the PubMed searches were subjected to screening to identify articles relevant to the targeted indication (hysterectomy) for further deeper analysis. The criteria, and rationale are presented in Table 5-3.

Table 5-3 Description of exclusion criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data pre-2007</td>
<td>Although the article was published after 2007 according to the search terms, the data referenced within cover a range prior to 2007</td>
</tr>
<tr>
<td>Articles with no abstract</td>
<td>At the level of top level screening, no informed decision regarding evidence or quality can be made without an abstract</td>
</tr>
<tr>
<td>Editorial/commentary</td>
<td>Articles that are commentaries or letters responding to other articles are not included for evidence recovery</td>
</tr>
<tr>
<td>Non-clinical</td>
<td>Articles which do not present any relevant clinical data, including patient surveys and experimental/ex vivo studies which were captured</td>
</tr>
<tr>
<td>Fewer than 20 patients</td>
<td>For higher quality evidence, studies of fewer than 20 patients are excluded</td>
</tr>
<tr>
<td>Non-targeted surgery</td>
<td>For a given surgical search area, if the focus of surgery of the article is for another, the study is excluded. Examples include the capture of mention of “bariatric procedures” for a study of appendectomy.</td>
</tr>
<tr>
<td>Not vessel-sealing focused</td>
<td>The mention of LigaSure™ or related technology is incidental and not the focus of the study with no data relevant to the performance of the technology</td>
</tr>
<tr>
<td>Not LigaSure™ technology</td>
<td>The reference by generic name to the technology cannot be conclusively identified as LigaSure™ at abstract level, or the reference to generic terms in the search such as electrocautery catches technology not relevant to bipolar vessel sealing</td>
</tr>
</tbody>
</table>
6. Data references


7. Geographical references


G23. Lafosse, A., Vandeputte, C., Sabor, I., Mahaudens, P. & Denoel, C. [About an extreme case of giant...


G41. Li, H., Wei, Y., Li, B. & Peng, B. Modified Thoracoscopic Hepatectomy For Segment VIII. Medicine (Baltimore) 95, e3801 (2016). (PMID: 27258516)


G87. Manouras, A. et al. Thyroid surgery: comparison between the electrothermal bipolar vessel sealing


G157. Fretland, A. A. *et al.* Open liver resection for colorectal metastases induced a significant increase in
interleukin-6 as compared to laparoscopic technique. *HPB* 16, 250–251 (2014).


G181. Kashintcev, A., Kochanenko, N. Y., Paveletc, K. V & Imyanitov, E. N. Comparison of dissection techniques


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