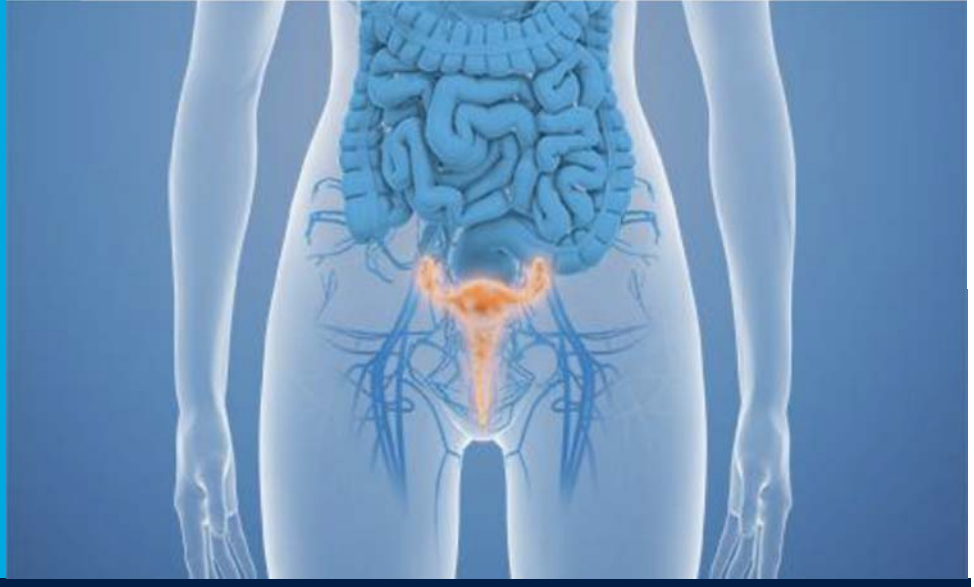

GLOBAL VALUE DOSSIER
FOR LIGASURE™ TECHNOLOGY
IN HYSTERECTOMY

Medtronic
Further, Together

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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™ 5 mm 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 LigaSure™ devices were derived from searches of published literature in PubMed (February 2017) and EMBASE (November 2016, May 2017). 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 7, 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

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, such as use of LigaSure™ technology. 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, and the current is provided in a smart algorithm by the energy platform, using tissue-sensing technology (TissueFect™,[a] technology a component of the LS10 generator and the ForceTriad™ and FT10 energy platforms) 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.

An accompanying dossier (LigaSure™ Technology GVD) is available detailing pre-clinical data and worldwide usage of LigaSure™ technology in clinical applications.

[a] White paper, Valleylab™ FT10 Energy Platform TissueFect™ Technology. McHenry J, Dunning J and Wagle K (2015) 10/2015 US150755[REF#479324]

3. Clinical evidence for LigaSure™ devices in hysterectomy[b]

3.1. Overview

Summary of LigaSure™ technology clinical evidence

- **Extensive global use:** Published reports of LigaSure™ device use in hysterectomy and associated gynecological procedures span 28 countries.[G1–G28]
- **Broad application:** LigaSure™ devices have been used in a range of procedures, including abdominal,[1] radical abdominal,[2] total laparoscopic,[3] laparoscopic supracervical,[4] laparoscopically-assisted vaginal[5] and vaginal[6] hysterectomy.
- **Decreased operative time:** LigaSure™ devices have been shown to significantly reduce the time of hysterectomy compared to suture ligation[2,5-9] and in comparison to other energy devices[c], has shown similar[4,10] and significantly reduced operative time.[11]
- **Low intraoperative blood loss:** The use of LigaSure™ devices has been shown to decrease the volume of blood lost during hysterectomy compared to suture ligation.[2,7,9] Compared to other energy devices[c], LigaSure™ technology has achieved similar[4,10] and significantly lower blood loss.[11]
- **Low post-operative pain:** The use of LigaSure™ devices compared to suture ligation has been shown to result in significantly lower pain in the days after surgery[7-9] and in fewer patients experiencing pain after the first post-operative week.[5]
- **Low complication rates:** LigaSure™ technology has been demonstrated to numerically reduce the risks of infection significantly[5] and non-significantly[1,5] after hysterectomy. LigaSure™ devices do not alter the risk of bladder injuries,[1,5,8] or overall risk of general post-surgical complications[1,5,9] associated with hysterectomy when compared to suture ligation.

*Note that statistical significance is not a direct indication of clinical relevance, which will be determined at the user's discretion.

3.2. The surgical area

The surgical removal of the uterus is a common gynecological procedure around the world. In the US alone in 2010, it was estimated that over 400,000 hysterectomies were performed as inpatient procedures.[12] The actual total number of hysterectomies is likely to be still higher, as the databases used in this study would fail to capture same-day discharges, leading especially to an underestimate of laparoscopic and robotic procedures.[12] The number of inpatient procedures per 100,000 inhabitants in 2010 for the US (140.2) is comparable to the upper end of the range across Europe in 2014 in countries for which data are available, from a minimum of 16.9 in Denmark, median Italy (100.2)/Croatia (102.7), to a maximum of 157.2 in the Czech Republic.[d]

Hysterectomies can be subdivided according to procedural details such as the extent of removal and the route of access (Table 3-1). Among described access routes in the US in 2010,[12] abdominal hysterectomy represented the primary means of access, similar to the

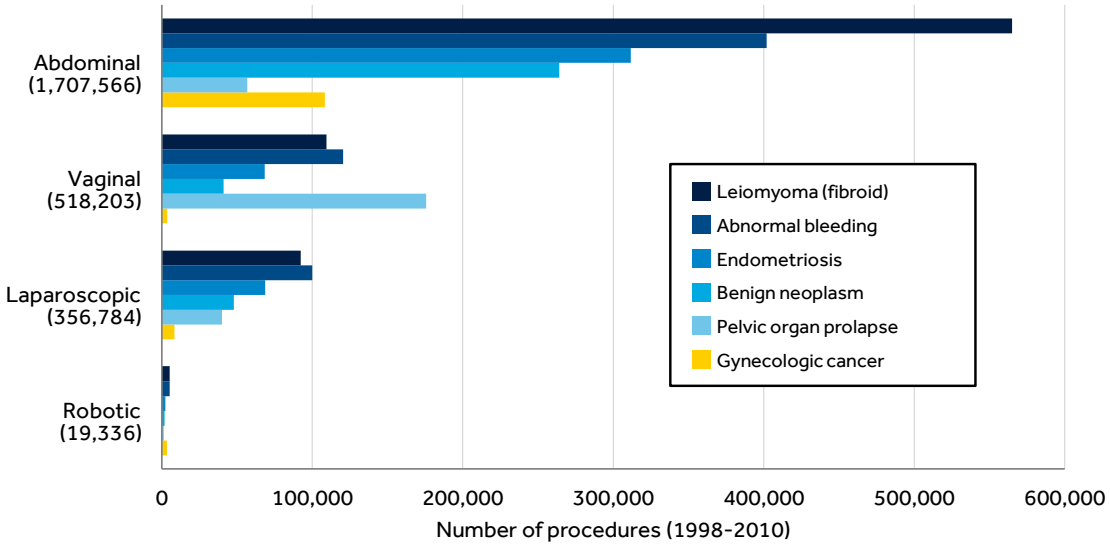
[b] Always refer to product labeling for indications for use of the associated LigaSure™ device (see section 1.1.)
[c] Other energy devices have included conventional and advanced energy bipolar, and harmonic scalpel.
[d] Eurostat table hlth_co_proc2, accessed 01 Mar 2017, available http://ec.europa.eu/eurostat/statistics-explained/index.php/Surgical_operations_and_procedures_statistics

situation in Europe.[d] Despite an overall decreasing trend in the number of hysterectomies performed, the proportion of those performed laparoscopically is on the rise; the US saw an approximately 3-fold increase from 2003 to 2010 (10% to 30%)[13] while across Europe the increase from 2009 to 2014 ranged from 10% in Poland, where the proportion of laparoscopic hysterectomies was already high (53% to 57%) to an increase of 460% in Romania where the procedure is less common (0.5% to 2.4%)[d].

Table 3-1 Selected types of hysterectomy

Type	Surgery	Description
AH	Abdominal hysterectomy	Removal of the uterus can be partial or total (TAH, total abdominal hysterectomy), removing the uterus and the cervix. The procedure is performed via abdominal access.
TLH	Total laparoscopic hysterectomy	Operative procedures (such as dissection of the uterine vessels) are performed laparoscopically, however the removal of the complete uterus can be via the vagina or in dissected segments via the laparoscopic ports.
VH	Vaginal hysterectomy	All operative procedures (division and sealing of blood vessels and tissues) are performed via vaginal access.
LAVH	Laparoscopically-assisted vaginal hysterectomy	Some of the operative procedures are performed laparoscopically and some vaginally. Removal of the uterus is via the vagina.
LSH	Laparoscopic supracervical hysterectomy	Also referenced as laparoscopic subtotal hysterectomy, the operative procedures are performed laparoscopically to remove the uterus, leaving the cervix intact.
RH/RAH	Radical hysterectomy/ Radical abdominal hysterectomy	Includes removal of uterus, cervix, and parts of vaginal support tissue (mostly for cancer indications). It may include bilateral salpingo-oophorectomy (BSO) where both fallopian tubes and ovaries are also removed. Can be performed abdominally or laparoscopically.

Figure 3-1 Hysterectomy access stratified by surgical indication



The data presented are cumulative for the United States spanning the period 1998-2010.[12] Bars indicate the number of procedures performed for the given indication, grouped by method of surgery/access. Numbers in parentheses indicate the total number of surgeries performed using the indicated method of access.

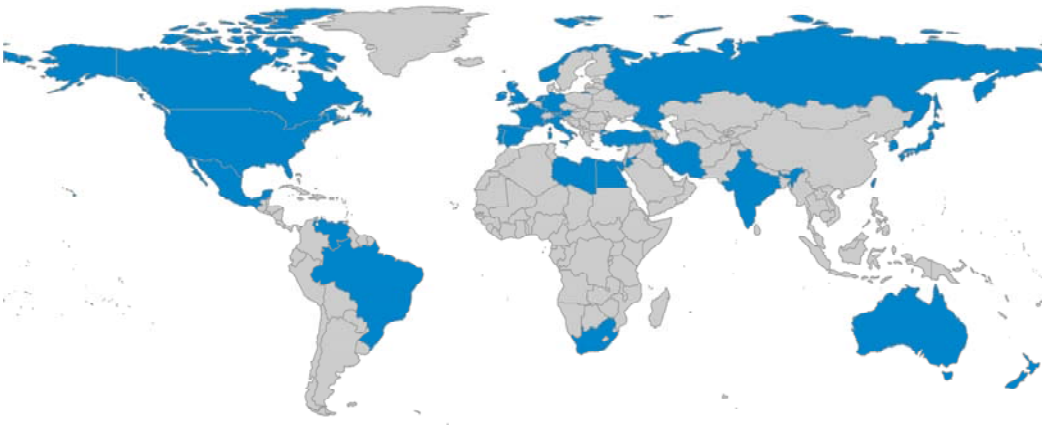
3.3. Diagnoses indicating hysterectomy

Hysterectomies are mainly performed for benign (non-cancerous) indications.[12] From a 2010 survey of data from the United States, leiomyomas (fibroids) were the most common indication for surgery while uterine cancer was the least frequent.[12] Over the period from 1998-2010, differences are seen in the route of access for the hysterectomy used for each of the associated indications (Figure 3-1).

3.4. LigaSure™ technology use in hysterectomy

LigaSure™ devices have been designed for use in any of the abovementioned types of hysterectomy and means of access. The technology has published references in 28 different countries across the world (Figure 3-2): Australia,[G1] Austria,[G2] Brazil,[G3] Canada,[G4] Egypt,[G5] France,[G6] Germany,[G7] India,[G8] Iran,[G9] Ireland,[G10] Italy,[G11] Jordan,[G12] Japan,[G13] Libya,[G14] Mexico,[G15] Netherlands,[G16] New Zealand,[G17] Norway,[G18] Portugal,[G19] Russia,[G20] South Africa,[G21] South Korea,[G22] Spain,[G23] Taiwan (Province of China),[G24] Turkey,[G25] United Kingdom,[G26] United States,[G27] and Venezuela.[G28] The subsequent sections report on peer-reviewed, published studies reporting clinical outcomes for LigaSure™ technology across the spectrum of devices and appropriate generators alone or in comparison to conventional means of surgical hemostasis, or other advanced energy devices.

Figure 3-2 Clinical use of LigaSure™ devices in hysterectomies



Highlighted are countries of origin for publications demonstrating the successful use of LigaSure™ technology in clinical settings across all types of hysterectomy.

3.5. LigaSure™ technology compared to conventional hemostasis

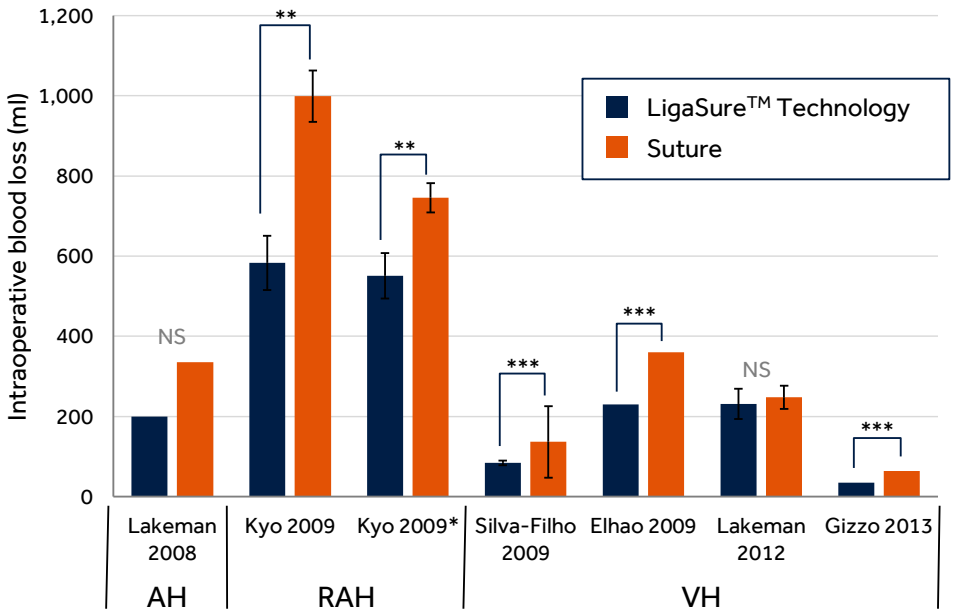
The uterus is supported by highly vascularized tissue and hemostasis is thus an important consideration during its removal. Conventional methods of hemostasis during hysterectomy are primarily mechanical consisting of clamping and sutures. Electrosurgical devices such as the bipolar vessel sealing of LigaSure™ technology were introduced to address unmet needs in surgical outcomes regarding blood loss, time (operative and hospital stay), and pain, among others. Studies reporting these outcome comparisons have been performed for all variants of hysterectomy access (abdominal, vaginal, and LAVH).

3.5.1. Blood loss

A major consideration for patient safety is the loss of blood that occurs during or after surgery. Blood loss can be assessed volumetrically[1,2,6-9] (for example by fluids delivered intraoperatively, Figure 3-3), decreases in hemoglobin[2,7,14] (Figure 3-4), or the need for blood transfusion[2,5,8] (Figure 3-5). Across volumetric measures of blood loss, LigaSure™ devices achieve mostly statistically significantly lower levels of blood loss, and comparable levels in the remaining studies. These results are consistent with the difference in pre- and post-operative hemoglobin measures, where LigaSure™ technology also achieves comparable to superior levels of intraoperative hemostasis compared to suture.

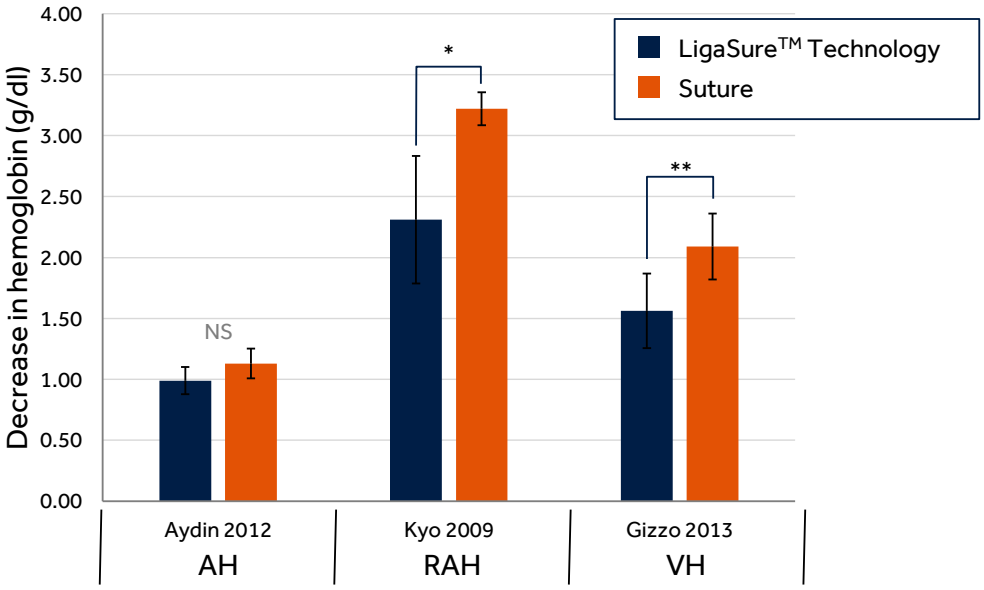
Comparative blood loss has also been assessed by meta-analysis,[15] confirming observations from the individual studies that the use of LigaSure™ devices results in reduced blood loss compared to sutures for some forms of hysterectomy (including radical abdominal,[2] peripartum abdominal,[16] and vaginal[6,7,9,16] hysterectomies). Where VH was considered alone by meta-analysis, LigaSure™ technology was found to significantly reduce operative blood loss ($p < 0.0001$ respectively) compared to sutures.[15]

Figure 3-3 Volume of intraoperative blood loss during hysterectomy with LigaSure™ devices versus suture ligation



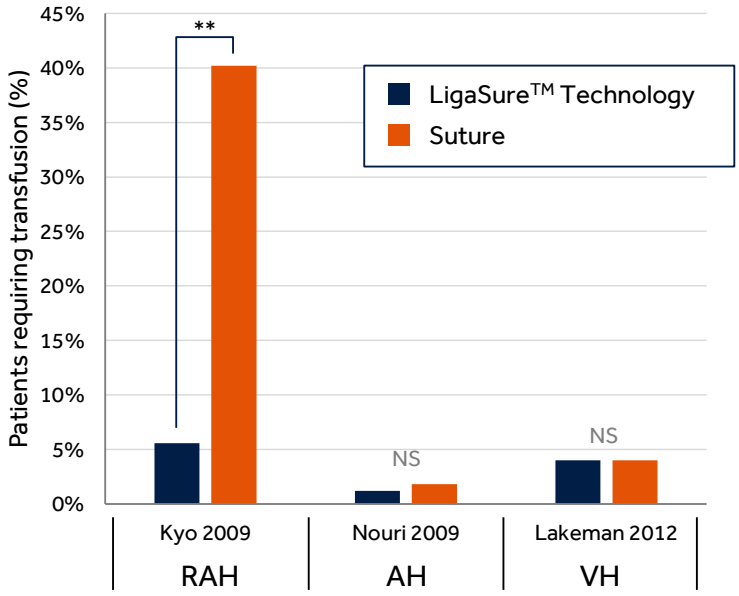
Reported results for volume of intraoperative blood loss for individual studies.[1,2,6-9] The type of hysterectomy performed is indicated below the study and error bars are the standard error of the mean (SEM) when present and otherwise not reported if absent. Statistical significance is indicated by p values (** = $p \leq 0.01$, *** = $p \leq 0.001$, NS, non-significant at the 95% confidence level). AH, abdominal hysterectomy; RAH, radical abdominal hysterectomy; VH, vaginal hysterectomy.

Figure 3-4 Intraoperative change in hemoglobin after hysterectomy with LigaSure™ devices versus suture ligation



Reported results for change in hemoglobin[2,7,14] (as a measure of intraoperative blood loss) for individual studies. The type of hysterectomy performed is indicated below the study and error bars are the standard error of the mean (SEM) when present and otherwise not reported if absent. Statistical significance is indicated by p values (* = $p \leq 0.05$, ** = $p \leq 0.01$, NS, non-significant at the 95% confidence level). AH, abdominal hysterectomy; RAH, radical abdominal hysterectomy; VH, vaginal hysterectomy.

Figure 3-5 Patients requiring blood transfusions after hysterectomy with LigaSure™ devices versus suture ligation



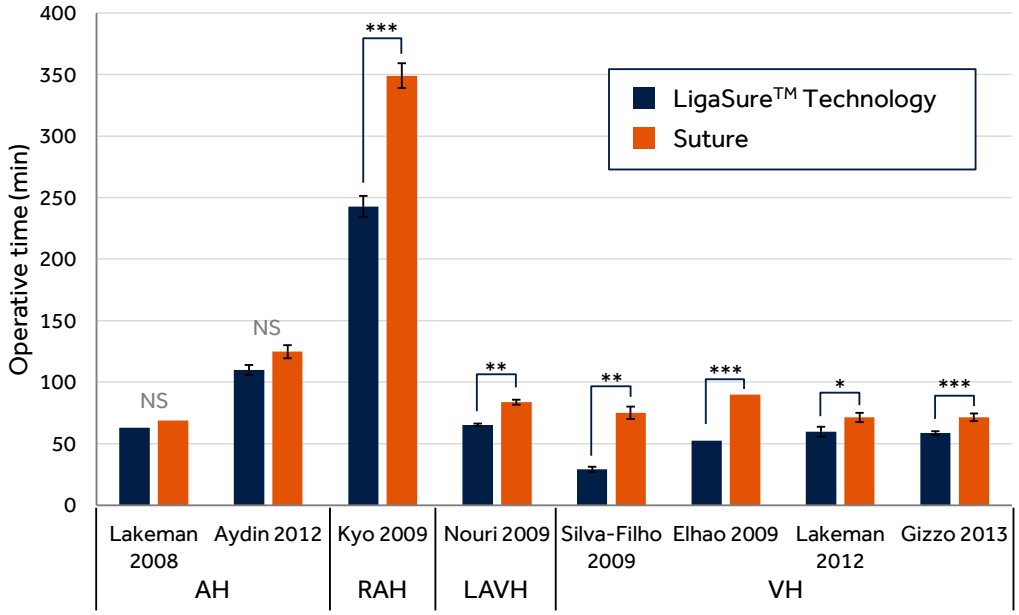
Results are shown from corresponding studies[2,5,8] as percentages of patients in the LigaSure™ technology and suture groups who required intraoperative blood transfusions. Values above the comparisons indicate statistical significance (** = $p \leq 0.01$, NS = not significant at the 95% confidence level). In the radical abdominal hysterectomy study of Kyo 2009[2] significance was calculated from the two tailed Chi-square test. AH, abdominal hysterectomy; NR, not reported; RAH, radical abdominal hysterectomy; VH, vaginal hysterectomy.

3.5.2. Time

Studies comparing LigaSure™ technology to conventional hemostasis often report on time relative to hospital resources. These include intraoperative time[1,2,5-9,14] (Figure 3-6), and overall length of stay in hospital[1,5,8,9,14] (Figure 3-7). In these comparisons, reported reductions in operative time with use of LigaSure™ technology are dependent upon the type of hysterectomy performed, with comparable results seen in abdominal hysterectomies and statistically significant reductions in operation times for radical abdominal and vaginal hysterectomies. Length of hospital stay is comparable between the two methods of hemostasis.

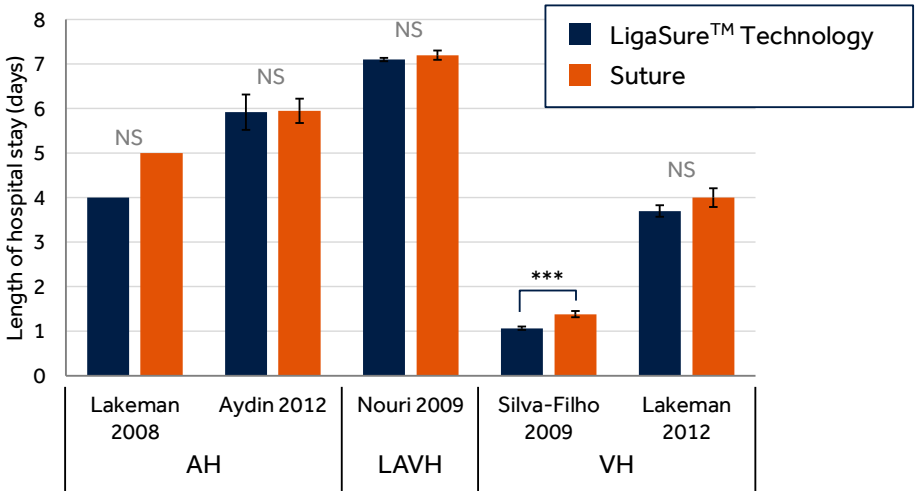
A single meta-analysis of operative time for VH[15] supports the observations of Figure 3-6, reporting a significant decrease in overall operation time ($p = 0.04$) compared to the use of sutures.

Figure 3-6 Duration of hysterectomy with LigaSure™ devices versus suture ligation



Results for operative time[1,2,5-9,14] are shown with reported significance above the bars(p values, * = p ≤ 0.05, ** = p ≤ 0.01, *** = p ≤ 0.001, NS = non-significant at the 95% confidence level). The type of hysterectomy performed is indicated below the study (name of first author and year of publication) and error bars are the standard error of the mean (SEM) when present and otherwise not reported if absent. AH, abdominal hysterectomy; LAVH, laparoscopically assisted vaginal hysterectomy; RAH, radical abdominal hysterectomy; VH, vaginal hysterectomy.

Figure 3-7 Length of hospital stay after hysterectomy with LigaSure™ devices versus suture ligation

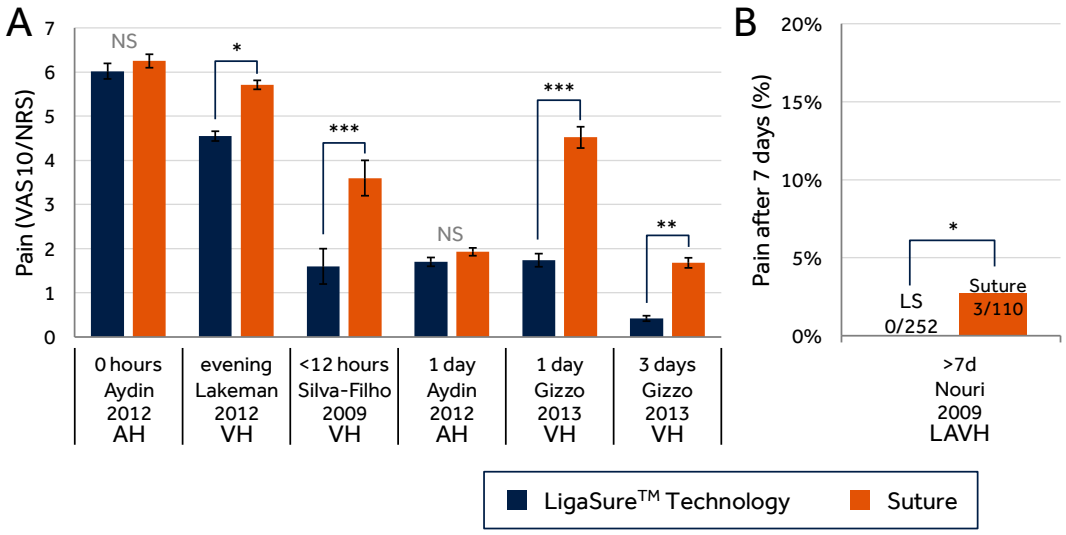


Results for length of hospital stay[1,5,8,9,14] are shown with reported significance above the comparisons (*** = p ≤ 0.001, NS = non-significant at the 95% level). The type of hysterectomy performed is indicated below the study (name of first author and year of publication) and error bars are the standard error of the mean (SEM) when present and otherwise not reported if absent. AH, abdominal hysterectomy; LAVH, laparoscopically assisted vaginal hysterectomy; VH, vaginal hysterectomy.

3.5.3. Procedure-associated pain

Studies reporting pain experienced by patients after hysterectomy have focused on the period from the time of surgery to just beyond the first post-operative week.[5,7-9,14] Early pain here is considered to be the day of or evening after surgery. Pain has been reported using the visual analog score (VAS) and numerical rating scales (NRS) for LigaSure™ devices versus suture use in the aforementioned time frame (Figure 3-8). The use of LigaSure™ devices has been associated with significantly lower early pain (the evening after surgery[8] and within the first 12 post-surgical hours[9]), and for reduced reports of pain beyond the first week.[5] For days over the first week, results are mixed with significant reductions in pain with LigaSure™ devices noted for individual days[7] and non-significant differences reported individually (day 1[14]) and broadly over the first week (p = 0.71, individual comparisons not reported[8]) compared to patients who received suture ligation.

Figure 3-8 Procedure-associated pain for LigaSure™ devices versus sutures

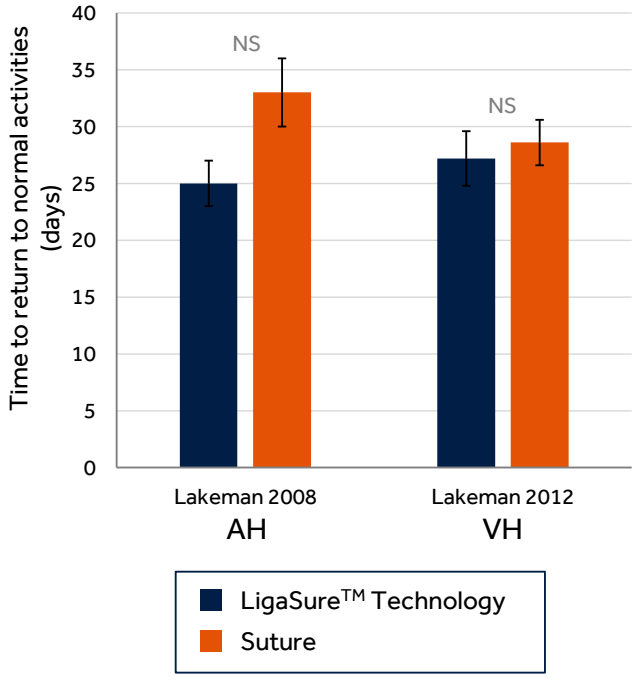


Pain scores were reported by patients at various times around hysterectomies performed with LigaSure™ devices or suture ligation. Scores were recorded (A) shortly before[14] (0h) the operation, the evening after[8] or within 12h[9] (<12h), one day (1d)[7,14] or three days (3d) post-surgery.[7] A separate study[5] (B) recorded rates of patients reporting pain after 1 week post-surgery. Values superimposed on bars indicate event counts reported of afflicted patients over the total number of patients in the study arm. Where no events occurred, the ligation method is also indicated. Statistical significance is shown above the comparisons (* = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, NS = non-significant at the 95% confidence level), and error bars represent the standard error of the mean (SEM). AH, abdominal hysterectomy; LAVH, laparoscopically assisted hysterectomy; LS, LigaSure™ device; NRS, numerical rating scale; VAS, visual analog scale; VH, vaginal hysterectomy.

3.5.4. Return to normal activities

A further measure of the patient experience is the record of the time taken to return to normal activities post-surgery[1,8] (Figure 3-9). After both AH[1] and VH[8] non-significantly shorter returns to normal activities have been reported with LigaSure™ devices compared to conventional ligation.

Figure 3-9 Time to return to normal activities after hysterectomy

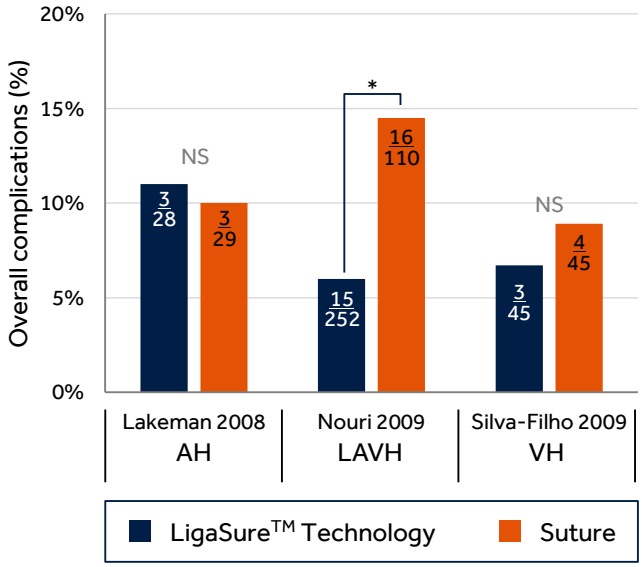


The time to return to normal activities was reported by patients receiving LigaSure™ device or suture ligation after AH[1] or VH[8] surgery. Statistical significance (NS = non-significant at the 95% confidence level) is indicated above the comparisons. Error bars represent the standard error of the mean (SEM). AH, abdominal hysterectomy; VH, vaginal hysterectomy.

3.5.5. Complication rates

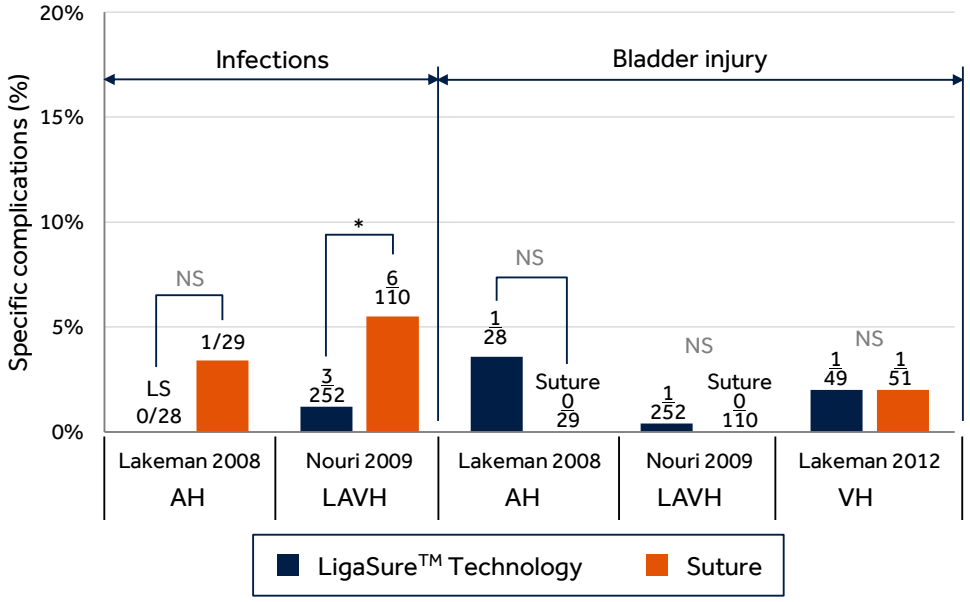
Studies vary in which complications are reported, noting for example whether an observed event may have been due to a previously existing condition and thus not related to the hysterectomy procedure. Examination of overall complication rates have shown similar[1,9] and significantly lower[5] rates of complications with the use of LigaSure™ devices compared to sutures (Figure 3-10). Infections[1,5] and bladder injuries (perforations[8] and lesions[5]) are among specific surgical complications that have been reported (Figure 3-11). Others which have been reported in one study[5] revealed no significant differences for bowel lesions, pulmonary emboli, or hemorrhages requiring reoperation.

Figure 3-10 Overall complication rates for LigaSure™ devices versus suture ligation in hysterectomy



Overall complication rates are shown as reported (including intra- and post-operative events as defined by study authors[1,5,9]). Values superimposed on bars indicate event counts of afflicted patients over the total number of patients in the study arm. Statistical significance is shown above the comparisons (* = p ≤ 0.05, NS = non-significant at the 95% confidence interval). AH, abdominal hysterectomy; LAVH, laparoscopically assisted vaginal hysterectomy; VH vaginal hysterectomy.

Figure 3-11 Rates for specific complications with LigaSure™ technology versus suture ligation in hysterectomy



Complication rates are shown for specific outcomes of infections[1,5] and bladder injuries (perforations[8] and lesions[5]). Values superimposed on bars indicate event counts of afflicted patients over the total number of patients in the study arm. Where there were no events, the ligation method is listed. Statistical significance is shown above the comparisons (* = p ≤ 0.05, NS = non-significant at the 95% confidence level. AH, abdominal hysterectomy; LAVH, laparoscopically assisted vaginal hysterectomy; VH vaginal hysterectomy.

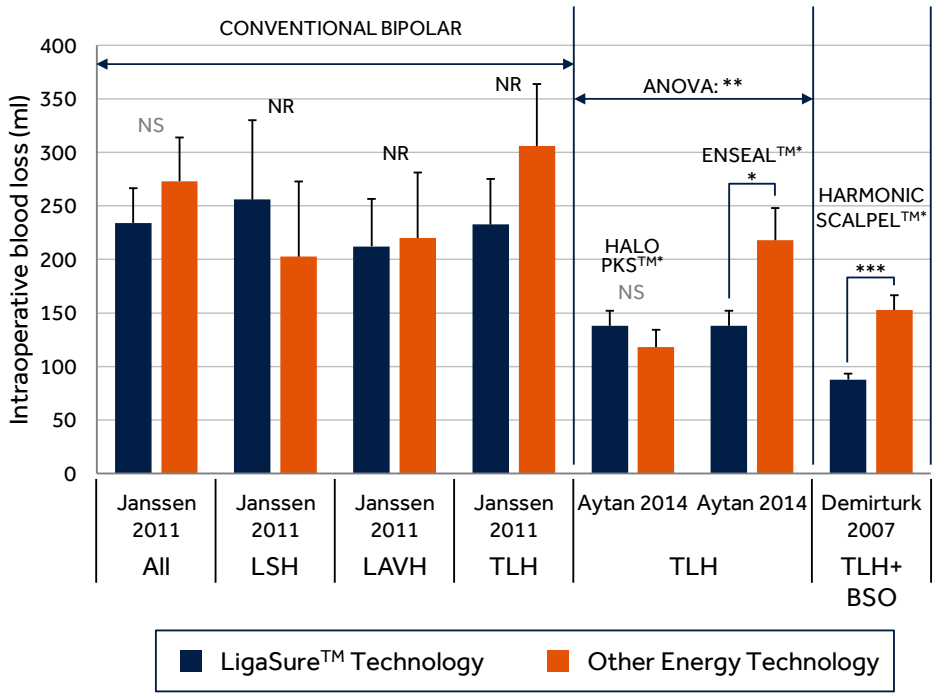
3.6. LigaSure™ technology compared to other advanced energy devices

As mentioned (Section 3.5) control of blood loss and associated outcomes are important considerations informing the method deployed during hysterectomy procedures. Surgical outcomes for LigaSure™ technology have also been compared to other energy-based vessel sealing devices (conventional[4] and other advanced energy[10,11]). These comparisons have been more restricted, occurring only in laparoscopic approaches to hysterectomy (TLH, LSH, and LAVH) and for outcomes focused on operative time and blood loss and length of hospital stay.

3.6.1. Blood loss

Comparisons of blood loss for LigaSure™ devices versus other energy devices (conventional and advanced energy) have been reported in terms of volumes of blood lost intraoperatively (Figure 3-12). Comparable results for LigaSure™ technology were obtained in comparisons with what was described as conventional bipolar sealing across multiple forms of laparoscopic hysterectomy, while significant reductions in blood loss were found in studies comparing LigaSure™ device use with Enseal™*, Halo PKS™*,[10] and with Harmonic Scalpel™*[11] for total laparoscopic hysterectomy.

Figure 3-12 Hysterectomy intraoperative blood loss of LigaSure™ technology versus other energy devices

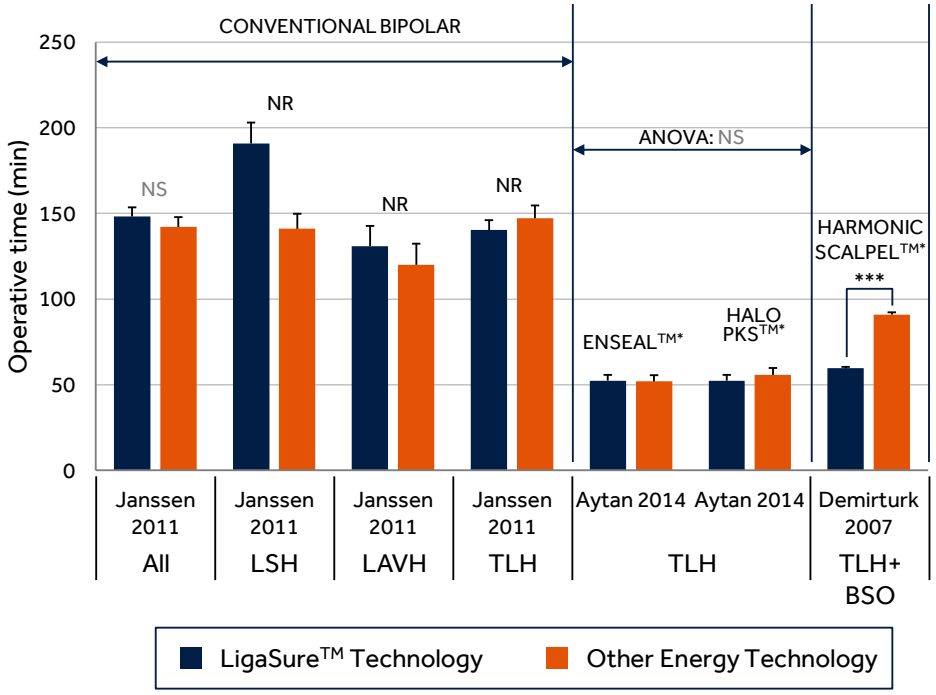


Reported intraoperative blood loss during laparoscopic hysterectomies for LigaSure™ devices versus conventional bipolar and other advanced energy devices. Statistical significance is indicated above comparisons (NR, not reported; NS, non-significant at the 95% confidence level; ** = p <0.01, *** = p <0.001). The Enseal™* and HALO PKS™* results were obtained in a single study[10] where significance was determined by analysis of variance (ANOVA) and post-hoc analysis. LAVH, laparoscopically assisted vaginal hysterectomy; LSH, laparoscopic supracervical hysterectomy; TLH, total laparoscopic hysterectomy; TLH+BSO, TLH plus bilateral salpingo-oophorectomy.

3.6.2. Time

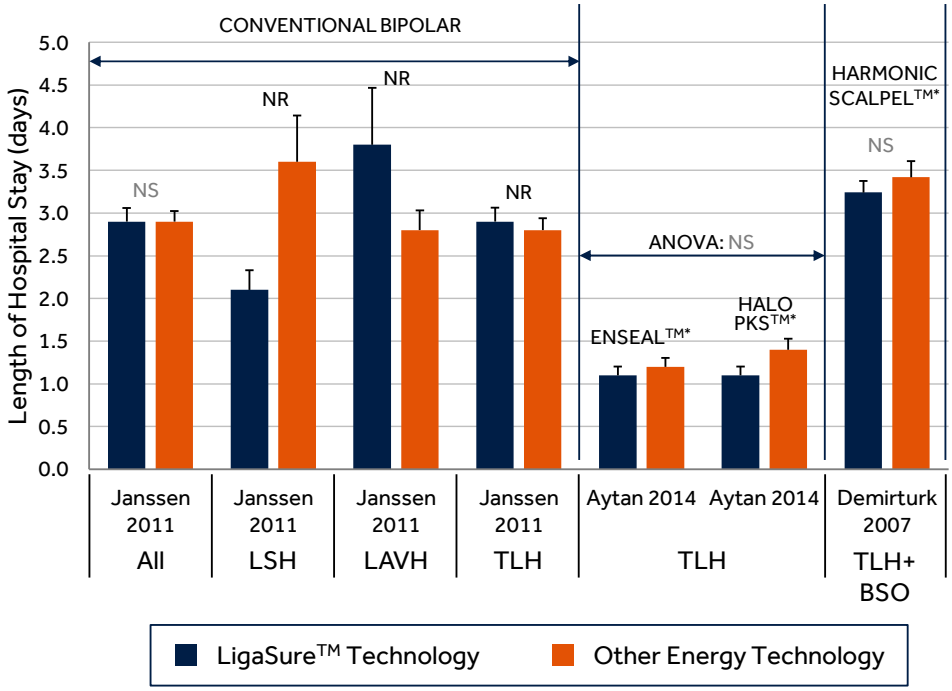
With respect to time measures related to hospital resources, studies comparing LigaSure™ devices to other energy devices have reported duration of operation[4,10,11] (Figure 3-13) and length of hospital stay[4,10,11] (Figure 3-14) results. The duration of laparoscopic hysterectomies is comparable for conventional bipolar, Enseal™* and Halo PKS™* devices across total and subtotal laparoscopic surgeries, and for laparoscopically assisted vaginal hysterectomy, however one study revealed a significant time savings for LigaSure™ technology compared to Harmonic Scalpel™* when TLH was combined with bilateral salpingo-oophorectomy.[11] Length of hospital stay across these surgery types was comparable across all devices.

Figure 3-13 Operative time for LigaSure™ technology and other energy devices used in hysterectomy



Reported operative time for patients undergoing laparoscopic hysterectomies with LigaSure™ devices versus conventional bipolar and other advanced energy devices. Statistical significance is indicated by p values above comparisons (NR, not reported; NS, non-significant at the 95% confidence level; *** = p <0.001). The Enseal™* and HALO PKS™* results were obtained in a single study[10] where significance was determined by analysis of variance (ANOVA) among the three devices. LAVH, laparoscopically assisted vaginal hysterectomy; LSH, laparoscopic supracervical hysterectomy; TLH, total laparoscopic hysterectomy; TLH+BSO, TLH plus bilateral salpingo-oophorectomy.

Figure 3-14 Length of hospital stay for LigaSure™ technology and other energy devices



Reported length of hospital stay for patients undergoing laparoscopic hysterectomies with LigaSure™ devices versus conventional bipolar and other advanced energy devices. Statistical significance is indicated by p values above comparisons (NR, not reported; NS, non-significant at the 95% confidence level). The Enseal™* and HALO PKS™* results were obtained in a single study[10] where significance was determined by analysis of variance (ANOVA) and individual comparisons between the LigaSure™ device and the other two were not made. LAVH, laparoscopically assisted vaginal hysterectomy; LSH, laparoscopic supracervical hysterectomy; TLH, total laparoscopic hysterectomy; TLH+BSO, TLH plus bilateral salpingo-oophorectomy.

4. Economic impact of LigaSure™ technology

4.1. Overview

Summary of LigaSure™ technology economic data

- **Procedure time and complications drive hysterectomy costs:** Hundreds of thousands of hysterectomy procedures are performed annually around the world.[12,e] Total costs can be influenced by operating room usage, and by costs of hysterectomy-specific complications.[8]
- **Procedure time with LigaSure™ devices is similar to reduced:** With significant reductions in surgical time compared to suture ligation ligation[2,5-9] and similar[4,10] and significantly reduced operative time[11] compared to harmonic scalpel, the use of LigaSure™ devices may result in costs associated with operation room usage.
- **Fewer to comparable complications with LigaSure™ device use:** The use of LigaSure™ devices compared to suture ligation has reported significantly reduced (infections and overall[5]) and equivalent rates of post-surgical complications.[1,5,8,9] Although such cost analyses have not been reported, LigaSure™ technology would thus be expected to be beneficial or cost-neutral compared to suture ligation for complications that incur costs for management.
- **Substantial cost savings reported with LigaSure™ devices:** In comparison to suture ligation, LigaSure™ devices provided per-procedure savings of $200 in hospital costs and $100 in staffing costs (2016 USD[f]).[8] When compared to reusable monopolar scissors, even when including costs of disposal of the single use device, LigaSure™ technology achieved savings of $900[f] for direct operating room costs and $270[f] in overall costs.[3]

4.2. Health economics of surgery

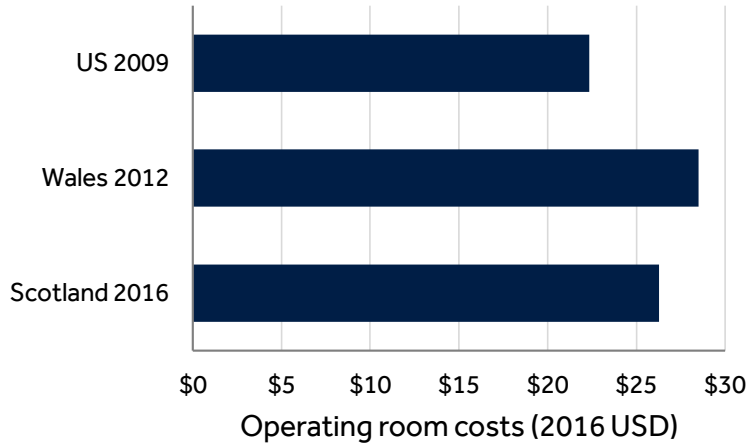
Worldwide, hysterectomy remains a prominent surgery with hundreds of thousands of procedures performed per year (see 3.2). Achieving efficiencies in the administration of hysterectomy thus has the potential to impact healthcare budgets and realize savings for payers.

As with any surgery, direct costs are incurred for consumables and hospital resources such as staffing and administration. Operating room costs vary by setting (Figure 4-1). Devices or changes to procedures that reduce operating room time per procedure thus have the potential to increase savings.

[e] Eurostat table hlth_co_proc2, accessed 01 Mar 2017, available http://ec.europa.eu/eurostat/statistics-explained/index.php/Surgical_operations_and_procedures_statistics

[f] Reported costs inflated to 2016 US dollars

Figure 4-1 Operating room costs per minute



Operating room costs per minute as reported in publications (US 2009 from estimate for basic surgical procedures,[17] Scotland 2016 from regional average[g] and Wales 2016 reported by a single NHS trust[h]). Corresponding values inflated to 2016 USD

4.3. Economics of hysterectomy

Specifically for hysterectomies, patient outcomes that have been reported can affect the direct costs include duration of operation, length of hospital stay and complications rates. The latter can influence costs both for intraoperative management such as the need for transfusion, or post-operatively if there is an unplanned readmission resulting from the surgery (Table 4-1). Intraoperatively, there are material costs such as those for the devices or other consumables, staff, and operating room costs.

Table 4-1 Reported hysterectomy-related complication costs,[8] Netherlands

Care	Unit	Cost (EUR)
Index admission and readmission, general ward	Day	€463
Blood – packed cells	Unit	€204
Reoperation vaginally	Session	€886
Reoperation abdominally	Session	€1,263
Outpatient general practitioner	Visit	€28
Outpatient hospital	Visit	€73
Emergency room	Visit	€153

Costs are shown as reported in 2011 EUR from the Netherlands.[8]

Health economic considerations include more than just costs. As a surgery that can have a large impact on a woman's life, analyses must include the patient experience and potential for disruption to her life, for example including complication rates and experienced pain.

[g] Table RX140X_2016, http://www.isdscotland.org/Health-Topics/Finance/Costs/Detailed-Tables/Theatres.asp
[h] Freedom of information request FoI.13.319, http://www.cardiffandvaleuhb.wales.nhs.uk/freedom-of-information-disclosure-log-20-2

4.4. LigaSure™ technology impact on hysterectomy

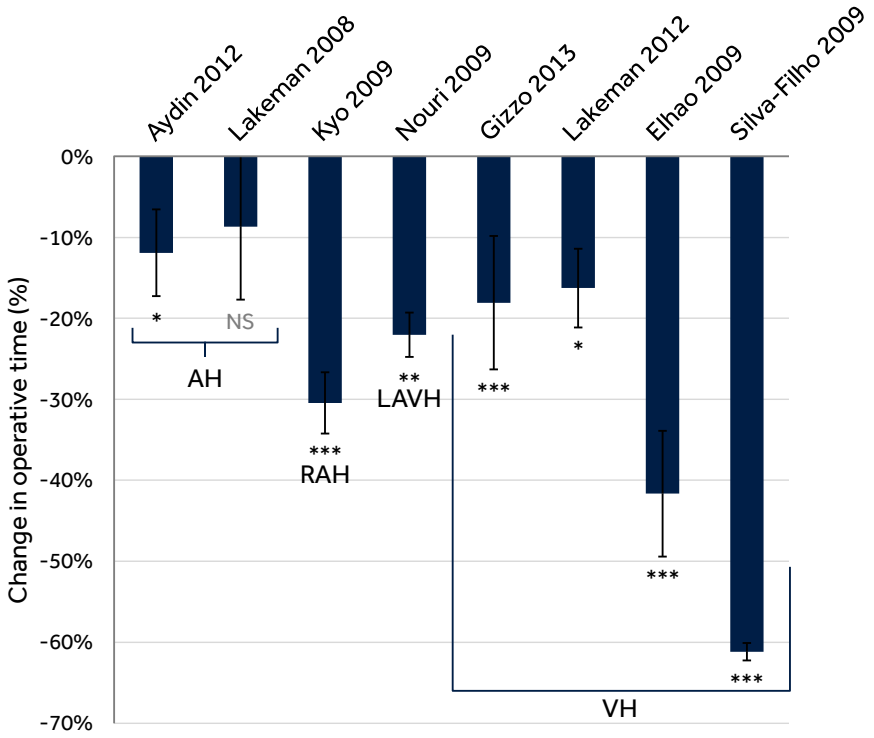
Few studies have reported direct cost data related to the use of LigaSure™ devices in hysterectomy versus conventional or other advanced energy devices. Choice of device or methodology will only impact on variable costs incurred by an institution per procedure[17] rather than the potentially high fixed costs such as facility rental or administration costs which remain fixed regardless of the nature or throughput of procedures. As described above, however, economic impact may be inferred from peri-operative parameters that influence variable costs such as the potential for reduction in blood loss (reducing need for transfusion), operative time, post-operative complications, and patient experience.[18]

4.4.1. LigaSure™ devices versus conventional ligation

Outcomes that can be more readily extrapolated to economic outcomes have been more frequently reported for LigaSure™ technology versus conventional suture ligation (see section 3.5). The statistically significant decreases in intraoperative blood loss observed for RAH[2] and VH[6-9] would result in lower blood product requirements during surgery.

Significant reductions in operative time could also be directly translated into cost savings. Exact savings would vary, as different surgeries require different lengths of time and different institutions will have a wide range of costs. Considered proportionally (Figure 4-2), the savings in time shown for LigaSure™ technology versus conventional suture for AH,[1,14] RAH,[2] LAVH,[5] and VH[6-9] could thus translate into similar percentage reduction in operating costs that directly result from operating room usage.

Figure 4-2 Time savings per procedure with LigaSure™ devices versus suture ligation



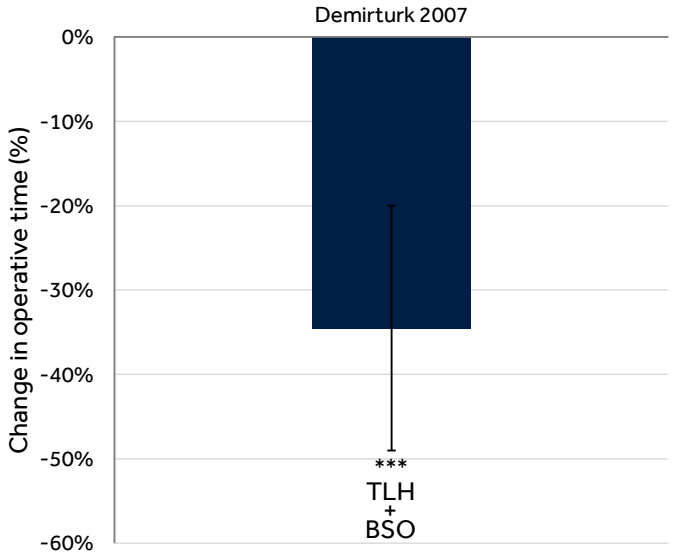
Shown are the proportional time savings using LigaSure™ devices instead of conventional sutures (decrease in operation duration as a percentage of surgery time using sutures) for AH,[1,14] RAH,[2] LAVH,[5] and VH.[6-9] Statistical significance as shown is as reported in the corresponding publications (* = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$; NS, non-significant). AH, abdominal hysterectomy; LAVH, laparoscopically assisted vaginal hysterectomy; RAH, radical hysterectomy; VH, vaginal hysterectomy.

4.4.2. LigaSure™ devices versus other energy devices

As seen in sections 3.6, many studies comparing LigaSure™ technology to other energy devices have combined results for different types of hysterectomy or for multi-arm comparisons with other devices. One study comparing LigaSure™ technology to conventional bipolar found no significant differences in measured outcomes across multiple forms of laparoscopic surgery (LSH, LAVH, and TLH) although these were not stratified for individual comparisons.[4] A further three-armed study investigated LigaSure™ devices compared to Enseal™* and Halo PKS™*,[10] however again did not separate comparisons for each device.

One remaining study compared LigaSure™ technology to Harmonic Scalpel™* for TLH with BSO[11] and in this context, significant differences were observed in reduced blood loss (Figure 3-12) and operative time (Figure 3-13). The observed reduction in surgical time of 34.5% of the time required for the operation with Harmonic Scalpel™* (Figure 4-3) is comparable to proportional reductions observed for other surgery typed in comparisons with conventional ligation (Figure 4-2). Exact cost savings would be dependent on individual hospitals.

Figure 4-3 Time savings per procedure with LigaSure™ devices versus Harmonic Scalpel™*

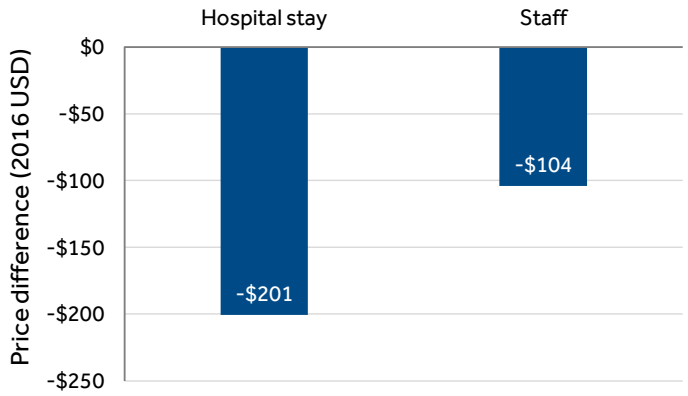


Proportional time savings from a single study comparing surgical times for a LigaSure™ device with Harmonic Scalpel™*.[11] The reduction in time was statistically significant (*** = p < 0.001). BSO, bilateral salpingo-oophorectomy; TLH, total laparoscopic hysterectomy.

4.4.3. Direct economic evaluation of LigaSure™ technology

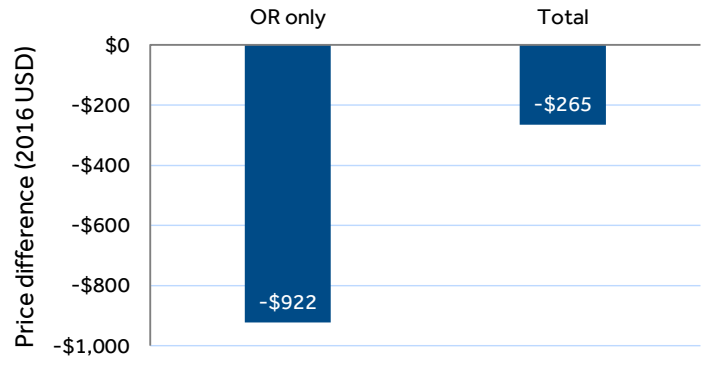
The extrapolations above from outcome changes (such as reduced operative time) have been directly characterized for the use of LigaSure™ technology versus conventional suture in VH[8] and for an alternative reusable monopolar electrosurgical device for laparoscopic procedures.[3] In both cases, the authors report overall cost savings per procedure. In the comparison with suture ligation (Figure 4-4), the increased costs of the device compared to sutures are offset by other intra- and perioperative savings for both AH[8] and in another study of LAVH.[5] In the latter analysis, the cost savings analysis of the single-use LigaSure™ device versus the reusable monopolar (Figure 4-5) included disposal and sterilization costs respectively, and included both resident and attending surgeons. The savings were primarily attributed to the time savings per procedure.

Figure 4-4 Reported cost savings LigaSure™ device versus suture



Original costs were reported in 2011 EUR from a study spanning 8 hospitals in the Netherlands.[8] These were converted to 2011 USD and inflated to 2016 USD. Cost savings were reported for total hospital stay and the portion thereof directly attributable to reduced staff costs. Ranges and standard deviations were not reported.

Figure 4-5 Reported cost savings LigaSure™ device versus monopolar device



Costs shown were inflated from 2013 USD (corresponding to the study period)[3] comparing the single-use LigaSure™ device to reusable monopolar scissors. Costs included disposal of the single-use and sterilization of the reusable devices and procedures were performed by resident and attending surgeons. Ranges and standard deviations were not reported. OR, operating room.

5. Conclusions

Hysterectomy is a major surgery that can have a large impact on a woman's life. Despite a trend over the last decade in decreasing numbers of procedures,[12,13] it remains a prominent surgery with hundreds of thousands of procedures per year worldwide. Over the same period, there has been a concomitant increase in changes to surgical procedures to reduce the trauma, notably in observed increases in minimally-invasive approaches to the procedure.[12,13,i] The choice of medical device employed during the procedure has also been shown to substantially impact the patient experience and healthcare budgets. In many peer-reviewed studies, use of LigaSure™ technology has significantly improved patient outcomes compared to suture ligation[2,6,7,9] and other energy devices.[11] This improvement is generally achieved at minimal or no additional cost to the healthcare provider.[3,5,8]

LigaSure™ technology for vessel dividing/sealing and tissue division is designed for intraoperative hemostasis. The devices and the associated power generators have been successfully applied in various settings around the world, and for a variety of surgeries. In hysterectomy, LigaSure™ technology has been used for abdominal,[1,14,16] radical abdominal,[2] laparoscopic (total[4,10,19-22] and supracervical[4]), vaginal[6-9,16,19] and laparoscopically assisted vaginal[4,5] operations.

Compared to suture technology, positive patient outcomes associated with the use of LigaSure™ devices have included decreased operation time,[1,2,5-9,14] decreased blood loss,[1,2,6-9] decreased early post-operative pain,[7-9,14] report of pain lasting longer than one week post-surgery,[5] and decreased complication rates (non-significant[1,9] and significant[5]). These benefits are apparent across the range of surgeries where the technology has been reported. Despite the higher device cost compared to suture, institutions using LigaSure™ technology have reported overall cost savings per procedure, driven by intraoperative time savings.[5,8]

Other advanced energy devices for vessel sealing are available, but fewer studies have compared these with LigaSure™ technology. Nevertheless, significant benefits of LigaSure™ devices were identified in studies which have compared LigaSure™ devices to conventional bipolar devices.[4] As well as significant reductions in blood loss with LigaSure™ technology, non-significant differences were reported in terms of intraoperative blood loss and surgical time in three-way comparisons[10] with Enseal™* and Halo PKS™*. Likewise, a direct comparison with a Harmonic Scalpel™* device[11] yielded statistically significant decreases in blood loss and operative time for LigaSure™ devices. Similar to comparison with conventional suture methods, LigaSure™ devices were also reported to generate cost savings when compared to a reusable monopolar device.[3] Even in consideration of device purchase and disposal costs, the use of LigaSure™ technology resulted in lower costs per procedure than the comparator.

Overall, where hysterectomy is indicated, LigaSure™ devices are a viable option. Use of LigaSure™ devices is supported by recent, peer-reviewed, published evidence demonstrating the potential for improved patient outcomes, and benefits to payers in reduced costs.

[i] Eurostat table hlth_co_proc2, accessed 01 Mar 2017, available http://ec.europa.eu/eurostat/statistics-explained/index.php/Surgical_operations_and_procedures_statistics

6. Source data tables

Refer to section 1.2 for scope of literature presented in the following data tables.

6.1. Data table summary: LigaSure™ technology surgical outcome data

Table 6-1 Publication data on LigaSure™ technology for clinical outcomes in hysterectomy

Source	Country	Study	Surgery	Device	Generator	Comparator	Outcomes	LigaSure™ Results	Comparator Results	P-value	Measure
Holloran-Schwartz MB, et al., 2016[3]	United States	RCT	TLH	Blunt tip LF1537	ForceTriad™	conv bipolar forceps	N	52	52		
							cutting time (min)	8.4	14.6	<0.001	med
Rossetti D, et al., 2015[16]	Italy	retro, cohort	PH (AH/VH)	NR	NR	conv (non-LS)	N	23	26		
							blood loss (ml)	1900 (700-4000)	2700 (800-8000)	0.001	Med(range)
							operative time (min)	110 (60-240)	170(85-320)	0.06	Med(range)
							LoS (days)	6 (4-9)	8 (5-10)	0.75	Med(range)
							overall complications (N)	1/23	1/26	0.92	Proportion
							transfusion (N, >10 U RBC)	6/23 (13%)	15/26 (27%)	0.025	Proportion
							postop complications (N)	6/23	4/26	0.35	Proportion

Source	Country	Study	Surgery	Device	Generator	Comparator	Outcomes	LigaSure™ Results	Comparator Results	P-value	Measure
Aytan H, et al., 2014[10]	Turkey	RCT	TLH	LS1537	NR	ENSEAL	N	15	15		Count
							blood loss (ml)	138.0 (54.3)	118.0 (63)	0.004 (ANOVA)	Mean(SD)
							operative time (min)	52.4 (12.9)	51.9 (14.1)	0.73 (ANOVA)	Mean(SD)
							LoS (days)	1.1 (0.4)	1.2 (0.4)	0.22 (ANOVA)	Mean(SD)
							reduction Hct (%)	4.2 (1.8)	5.26 (2.2)	0.37 (ANOVA)	Mean(SD)
							reduction Hb (g/dl)	1.3 (0.6)	1.6 (0.7)	0.40 (ANOVA)	Mean(SD)
						HALO PKS	N	15	15		Count
							blood loss (ml)	138.0 (54.3)	218.0 (115.9)	0.004 (ANOVA)	Mean(SD)
							operative time (min)	52.4 (12.9)	55.7 (15.7)	0.73 (ANOVA)	Mean(SD)
							LoS (days)	1.1 (0.4)	1.4 (0.5)	0.22 (ANOVA)	Mean(SD)
							reduction Hct (%)	4.2 (1.8)	4.9 (2.2)	0.37 (ANOVA)	Mean(SD)
							reduction Hb (g/dl)	1.3 (0.6)	1.5 (0.7)	0.40 (ANOVA)	Mean(SD)
Pergialiotis V, et al., 2014[15]	Greece*	MA	VH	NR	NR	suture	N	268	269		Count
							blood loss (ml)	-48.94 [-68.88,-29.00]	0	<0.0001	Mean[CI]
							operative time (min)	-20.77 [-40.54, -1.01]	0	0.04	Mean[CI]

Source	Country	Study	Surgery	Device	Generator	Comparator	Outcomes	LigaSure™ Results	Comparator Results	P-value	Measure
Gizzo S, et al., 2013[7]	Italy	prosp	VH	LS Auto	NR	suture	N	21	21		Count
							blood loss (ml)	34.29 (14.34)	63.81 (32.82)	<0.001	Mean(SD)
							operative time (min)	58.52 (7.34)	71.43 (14.11)	<0.001	Mean(SD)
							pain early (day1 NRS)	1.69 (1.56)	4.5 (2.51)	<0.001	Mean(SD)
							pain early (day3 NRS)	0.43 (1.67)	0.598 (1.165)	<0.01	Mean(SD)
							postop Hb (g/L)	122.38 (9.92)	114.62 (8.7)		Mean(SD)
							preop Hb (g/L)	138.00 (9.88)	135.52 (8.81)		Mean(SD)
							reduction Hb (g/dl)	15.62	20.9	<0.01	NR
Aydin C, et al., 2012[14]	Turkey	RCT	AH	NR	NR	suture	N	44	44		Count
							operative time (min)	109.91 (26.55)	124.77 (35.51)	0.029	Mean(SD)
							LoS (days)	5.92 (2.63)	5.95 (1.82)	0.949	Mean(SD)
							pain early (0h, VAS)	6.02 (1.17)	6.25 (1.01)	0.333	Mean(SD)
							pain early (1d, VAS)	1.70 (0.66)	1.93 (0.58)	0.093	Mean(SD)
							reduction Hb (g/dl)	0.99 (0.74)	1.13 (0.81)	0.328	Mean(SD)
Lakeman MM, et al., 2012[8]	The Netherlands	RCT	VH	NR	NR	suture	N	49	51		Count
							blood loss (ml)	231.4 (263.4)	247.7 (206.4)	0.74	Mean(SD)
							operative time (min)	59.7 (28.3)	71.3 (27.0)	0.05	Mean(SD)
							LoS (days)	3.7 (0.9)	4.0 (1.5)	0.2	Mean(SD)
							pain <1wk (VAS)	NA	NA	0.71	NR
							pain evening after proc (VAS)	45.5 (1.1)	57.1 (1.0)	0.02	Mean(SEM)
							time to normal	27.2 (2.4)	28.6 (2.0)	0.66	Mean(SEM)
							complication bladder lesion (N)	1 (2%)	1 (2%)	1	Proportion
							complication, blood loss > 500ml (N)	3 (6%)	3 (6%)		Proportion
							transfusions (N)	2 (4%)	2 (4%)	1	Proportion

Source	Country	Study	Surgery	Device	Generator	Comparator	Outcomes	LigaSure™ Results	Comparator Results	P-value	Measure
Janssen PF, et al., 2011[4]	The Netherlands	RCT	Comb (AH + VH)	LV 1500 V	NR	conv bipolar knife	N	66	65		Count
							blood loss (ml)	234.1 (263)	273.1 (329)	0.46	Mean(SD)
							operative time (min)	148.2 (43.6)	142.1 (46.1)	0.46	Mean(SD)
							LoS (days)	2.9 (1.3)	2.9 (1.0)	0.94	Mean(SD)
							adnexal ligament dissection (min)	2m37s (2m10s)	4m33s (5m1s)	0.02	Mean(SD)
			LASH	LV 1500 V	NR	conv bipolar knife	N	12	11		Count
							blood loss (ml)	255.8 (257)	202.5 (233)		Mean(SD)
							operative time (min)	190.8 (42.5)	141.0 (29.2)		Mean(SD)
							LoS (days)	2.1 (0.8)	3.6 (1.8)		Mean(SD)
							adnexal ligament dissection (min)	1m56s (1m46s)	1m04s (0m54s)		Mean(SD)
			LAVH	LV 1500 V	NR	conv bipolar knife	N	9	12		Count
							blood loss (ml)	212.2 (133)	220 (212)		Mean(SD)
							operative time (min)	130.9 (35.5)	120.0 (42.9)		Mean(SD)
							LoS (days)	3.8 (2.0)	2.8 (0.8)		Mean(SD)
							adnexal ligament dissection (min)	2m12s (1m24s)	3m50s (5m01s)		Mean(SD)
			TLH	LV 1500 V	NR	conv bipolar knife	N	45	42		Count
							blood loss (ml)	232.6 (286)	305.9 (375)		Mean(SD)
							operative time (min)	140.3 (39.0)	147.2 (48.7)		Mean(SD)
							LoS (days)	2.9 (1.1)	2.8 (0.9)		Mean(SD)
							adnexal ligament dissection (min)	2m51s (2m21s)	5m34s (5m18s)		Mean(SD)

Source	Country	Study	Surgery	Device	Generator	Comparator	Outcomes	LigaSure™ Results	Comparator Results	P-value	Measure
Elhao M, et al., 2009[6]	Egypt	RCT	VH (DF)	LS Max	LVSGen	suture	N DF	24	25		Count
							blood loss (ml) DF	270 (130-555)	425 (90-4800)	<0.024	Med(range)
							operative time (min) DF	72.5 (30-125)	100 (65-240)	<0.001	Med(range)
							postop Hct (%) DF	31.2 (4.4)	28.5 (4.3)	0.025	Mean(SD)
							postop Hb (g/dl) DF	9.7 (1.8)	8.8 (1.4)	0.054	Mean(SD)
			VH (SF)	LS Max	LVSGen	suture	N SF	26	28		Count
							blood loss (ml) SF	190 (40-690)	290 (120-500)	0.453	Med(range)
							operative time (min) SF	50 (25-75)	75 (50-95)	<0.001	Med(range)
							postop Hct (%) SF	32.8 (5.0)	29.4 (4.3)	0.006	Mean(SD)
							postop Hb (g/dl) SF	10.1 (1.4)	9.7 (1.3)	0.226	Mean(SD)
			VH (tot)	LS Max	LVSGen	suture	N tot	50	53		Count
							blood loss (ml) tot	230 (40-690)	360 (90-4800)	<0.001	Med(range)
							operative time (min) tot	52.5 (25-125)	90 (50-240)	<0.001	Med(range)
							postop Hct (%) tot	32 (4.8)	28.9 (4.3)	<0.001	Mean(SD)
							postop Hb (g/dl) tot	9.9 (1.6)	9.3 (1.4)	0.033	Mean(SD)
Kyo S, et al., 2009[2]	Japan	retro	AH (radical)	LS Precise LS Max	LVSGen	suture	N	18	67		
							blood loss (ml)	583.1 (287.6)	999.0 (524.2)	<0.005	Mean(SD)
							blood loss (ml) non-transfused	550.9 (233.1)	745.49 (230.4)	<0.01	Mean(SD)
							operative time (min)	242.8 (36.1)	349.1 (82.6)	<0.001	Mean(SD)
							transfusions (N)	1 (5.6%)	27 (40.2%)		Proportion
							reduction Hb (g/dl)	2.31 (2.22)	3.22 (1.11)	<0.05	Mean(SD)

Source	Country	Study	Surgery	Device	Generator	Comparator	Outcomes	LigaSure™ Results	Comparator Results	P-value	Measure
Nouri K, et al., 2009[5]	Austria	retro, case control	LAVH	NR	NR	suture	N	252	110		Count
							operative time (min)	65.28 (16.33)	83.73 (21.53)	<0.005	Mean(SD)
							LoS (days)	7.1 (0.6)	7.2 (1.1)	ns	Mean(SD)
							pain after 7d (N)	0 (0%)	3 (2.7%)	0.028	Proportion
							overall complications (N)	15 (6.0%)	16 (14.5%)	0.05	Proportion
							complications, bladder lesion (N)	1 (0.4%)	0 (0%)	1	Proportion
							complications, bowel lesion (N)	1 (0.4%)	0 (0%)	1	Proportion
							complications, pulmonary embolus (N)	1 (0.4%)	0 (0%)	1	Proportion
							transfusions (N)	3 (1.2%)	2 (1.8%)	0.643	Proportion
							complications, hemorrhage (N)	1 (0.4%)	2 (1.8%)	0.22	Proportion
							complications, infection (N)	3 (1.2%)	6 (5.5%)	0.025	Proportion
Silva-Filho AL, et al., 2009[9]	Brazil	RCT	VH	NR	NR	suture	N	45	45		Count
							blood loss (ml)	84 (5.9)	136.4 (89.1)	0.001	Mean(SEM)
							operative time (min)	29.2 (2.1)	75.2 (5)	<0.001	Mean(SEM)
							LoS (hours)	25.6 (0.9)	33.2 (1.7)	<0.001	Mean(SEM)
							pain (<12h, VAS 10)	1.6 (0.4)	3.6 (0.4)	<0.001	Mean(SEM)
							overall complications (N)	3 (6.7%)	4 (8.9%)	1	Proportion

Source	Country	Study	Surgery	Device	Generator	Comparator	Outcomes	LigaSure™ Results	Comparator Results	P-value	Measure
Lakeman M, et al., 2008[1]	The Netherlands	RCT	AH	NR	NR	suture	N	28	29		Count
							blood loss (ml)	200 (33-1500)	335 (40-1750)	0.08	Med(range)
							operative time (min)	63 (38-124)	69 (29-130)	0.62	Med(range)
							LoS (days)	4 (2-32)	5 (3-11)	0.26	Med(range)
							return to normal activities (days)	25 (2)	33 (3)	0.07	NR
							postop complications (any) (N)	3 (11%)	3 (10%)	0.96	Proportion
							complications, bladder lesion (N)	1 (3.6%)	0 (0%)		Proportion
							complications, blood loss >1l (N)	2 (7%)	3 (10%)		Proportion
							complications, infection (N)	0 (0%)	1 (3.4%)	0.96	Proportion
Demirturk F, et al., 2007[11]	Turkey	retro	TLH (radical)+ BSO	LS Atlas	NR	Harmonic Scalpel™* (Ultracision)	N	21	19		Count
							blood loss (ml)	87.76 (25.48)	152.63 (60.90)	<0.001	Mean(SD)
							operative time (min)	59.57 (3.71)	90.95 (5.73)	<0.001	Mean(SD)
							LoS (days)	3.24 (0.62)	3.42 (0.82)	0.436	Mean(SD)
							reduction Hct (%)	2.59 (3.03)	5.90 (3.03)	0.004	Mean(SD)
							reduction Hb (g/dl)	1.17 (1.15)	2.12 (1.38)	0.024	Mean(SD)

Overall complication rates are shown when reported and include peri- and post-operative complications. Units of "N" indicate counts for proportions (patients experiencing an event divided by total number of patients in that group). The study of Elhao et al., 2009[6] divided vaginal hysterectomy into difficult (DF) and straightforward (SF) procedures, and also analyzed all results together (tot). Countries indicated with an asterisk (*) are the origin of publication for meta analyses and thus do not directly represent usage of LigaSure™ technology in that setting. AH, abdominal hysterectomy; ANOVA, analysis of variance; BSO, bilateral salpingo-oophorectomy; CI, 95% confidence interval; comb, combination (abdominal and vaginal hysterectomy not separated), conv, conventional ligation; DF, (vaginal hysterectomy classified as) difficult; Hb, hemoglobin; Hct, hematocrit; LASH, laparoscopic supracervical hysterectomy; LAVH, laparoscopically assisted hysterectomy; LoS, length of stay; LS, LigaSure™; LS Auto, LigaSure™ Autosuture; LVSGen, LigaSure™ vessel sealing system generator; Med, median; NR, not reported; NRS, numerical rating scale; PH, perinatal hysterectomy; postop, post-operative; preop, pre-operative; prosp, prospective study; proc, procedure; RCT, randomized controlled trial; retro, retrospective study; SD, standard deviation; SEM, standard error of the mean; SF, (vaginal hysterectomy classified as) straightforward; SMD, standardized mean difference; TLH, total laparoscopic hysterectomy; tot, total; U RBC, (transfused) units of red blood cells; VAS, visual analog scale; VH, vaginal hysterectomy

6.2. Data table summary: LigaSure™ technology economic data

Table 6-2 Publication data on economics related to LigaSure™ technology use

Source	Country	Study	Surgery	Device	Generator	Comparator	Outcomes	LigaSure™ Result	Comparator Result	P-value	Measure
Holloran-Schwartz MB, et al., 2016[3]	United States	RCT	TLH	Blunt tip LF1537	ForceTriad™	conv bipolar forceps	cost savings (2013 USD, OR only)	-884.92			NR
							cost savings (2013 USD, tot)	-254.16			NR
Lakeman MM, et al., 2012[8]	The Netherlands	RCT	VH	NR	NR	suture	costs (hospital stay)	1,713	1,852		NR
							costs (staff)	616	688		NR
							costs (tot inpatient)	3,102 (2,958-3,250)	2,903 (2,651-3,225)	0.257	Mean[CI]
Nouri K, et al., 2009[5]	Austria	retro, case control	LAVH	NR	NR	suture	costs (direct material)	310	110		NA
Silva-Filho AL, et al., 2009[9]	Brazil	RCT	VH	NR	NR	suture	suture packs required	1.2 (0.6)	7.4 (0.3)	<0.001	Mean[SEM]

CI, 95% confidence interval; Comp, comparator; NR, not reported; OR, operating room; RCT, randomized controlled trial; retro, retrospective study; SEM, standard error of the mean; TLH, total laparoscopic hysterectomy; USD, United States dollars; VH, vaginal hysterectomy

7. Structured literature search details

7.1. 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) in hysterectomy procedures, 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 search was performed on February 27, 2017.

Table 7-1 Structured searched in PubMed to identify relevant LigaSure™ technology data

Index	Aim	Search string	Hits
#1	LigaSure™ by product name	ligasure*[tiab] OR ligasuretm[tiab] OR ligasurev*[tiab]	614
#2	Generic names for LigaSure™	EBVS[tiab] OR BVSS[tiab] OR ((bipolar[tiab] OR ((high[tiab] OR advanced[tiab]) AND energy[tiab]) OR radiofrequency[tiab]) AND (diathermy[tiab] OR cautery[tiab] OR electrocautery[tiab] OR electrocauterization[tiab] OR electrocauterisation[tiab] OR cauterization[tiab] OR cauterisation[tiab] OR coagulation[tiab] OR ((vessel[tiab] OR tissue[tiab]) AND (sealing[tiab] OR sealer[tiab]))))) OR electrosurgical[tiab] OR electrocoagulation[tiab] OR electrocoagulation[MeSH]	16,742
#3	Publication years of interest	"2007/01/01"[PDat]:"2018/12/31"[PDat]	9,418,446
#4	Invalid publication types	"Case Reports" [ptyp] OR "Clinical Conference" [ptyp] OR "Comment" [ptyp] OR "Editorial" [ptyp] OR "Letter"[ptyp] OR "Retracted Publication"[ptyp] OR "Congresses"[ptyp] OR "Duplicate Publication"[ptyp]	3,240,780
#5	Non-clinical data	"ex vivo"[tiab] OR cadaver[tiab] OR "deceased donor"[tiab]	78.271
#6	Animal data	Search terms for animal studies[23]	6,291,401
#7	LigaSure™ (by name or generic), restricted to publication years, excluding animal, non-clinical, and non-primary data	(#1 OR #2) AND #3 NOT (#4 OR #5 OR #6)	3,656
#8	All hysterectomy	(hysterectomy[tiab] OR hysterectomy[MeSH] OR "hysterectomy,vaginal"[MeSH]) AND (surgery[tiab] OR "surgical procedure"[tiab] OR "General Surgery"[Mesh] OR "Surgical Procedures, Operative"[Mesh])	34,056
#9	LigaSure™ + hysterectomy	#7 AND #8	136

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 7-2). 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.

Table 7-2 Structured search in EMBASE to identify use of LigaSure™ devices

Index	Aim	Search string	Hits
1	LigaSure™-specific technology (referenced by name) excluding ex vivo data and select animals	((ligasure or ligasurev or ligasuretm) not (preclinical or "ex vivo" or cadaver or animal or dog or cat or pig or veterinary or veterinarian)).mp.	1,390

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.

7.2. Screening literature results

7.2.1. Screening general search (EMBASE) results

The purpose of the EMBASE search as described (Section 7.1) 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.

7.2.2. 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 7-3.

Table 7-3 Description of exclusion criteria

Criterion	Explanation
Data pre-2007	Although the article was published after 2007 according to the search terms, the data referenced within cover a range prior to 2007
Articles with no abstract	At the level of top level screening, no informed decision regarding evidence or quality can be made without an abstract
Editorial/commentary	Articles that are commentaries or letters responding to other articles are not included for evidence recovery
Non-clinical	Articles which do not present any relevant clinical data, including patient surveys and experimental/ex vivo studies which were captured
Fewer than 20 patients	For higher quality evidence, studies of fewer than 20 patients are excluded
Non-targeted surgery	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.
Not vessel-sealing focused	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
Not LigaSure™ technology	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

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