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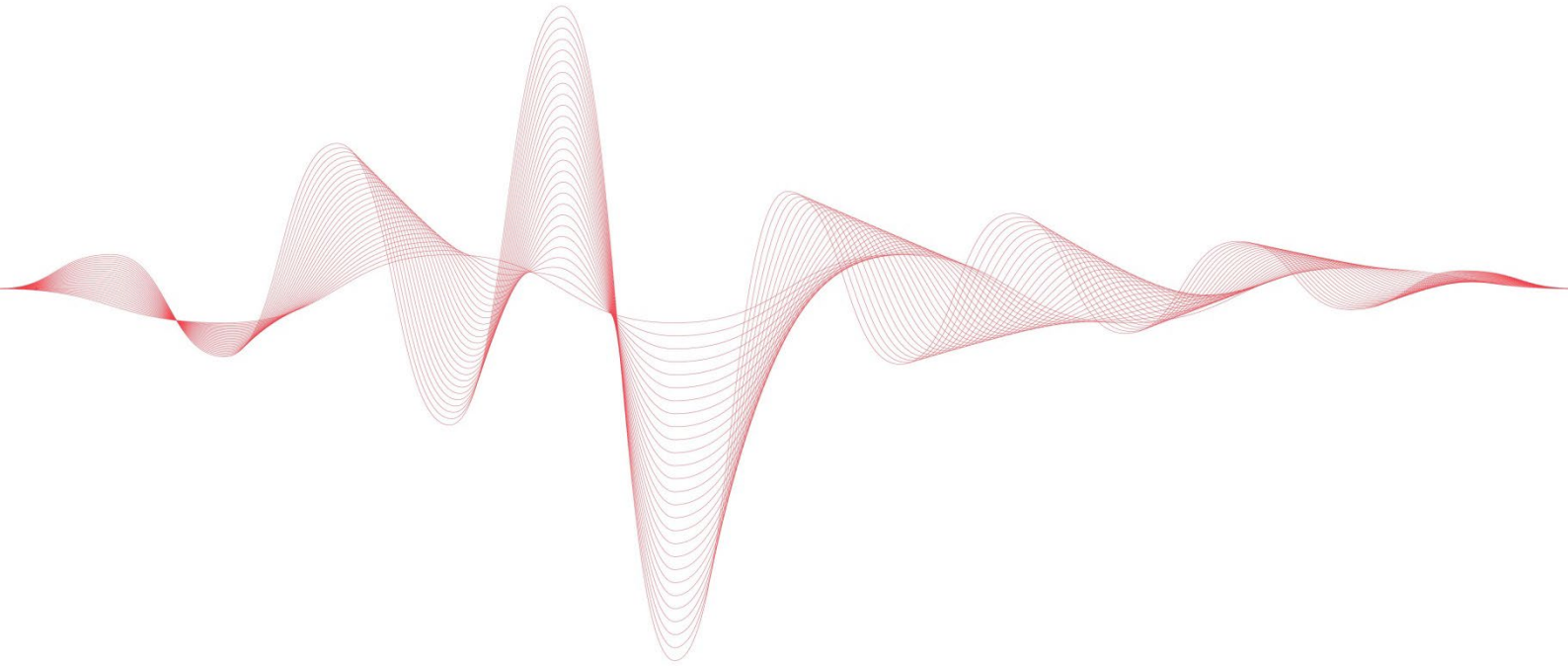
Provox® Voice Prostheses Literature Review

2019



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1 Introduction

During a total laryngectomy, the entire voice box is removed; the trachea is bent forward and sutured to the anterior neck, ending in a tracheostoma. The remainder of the pharynx is closed to restore the digestive tract. Depending on the extent and location of the tumor, more extensive resection (pharyngolaryngectomy or pharyngolaryngoesophagectomy) and reconstruction may be necessary. The three main methods of voice rehabilitation available to the laryngectomized patient are the use of an electrolarynx, esophageal speech, and tracheoesophageal speech using a voice prosthesis (Figure 1).

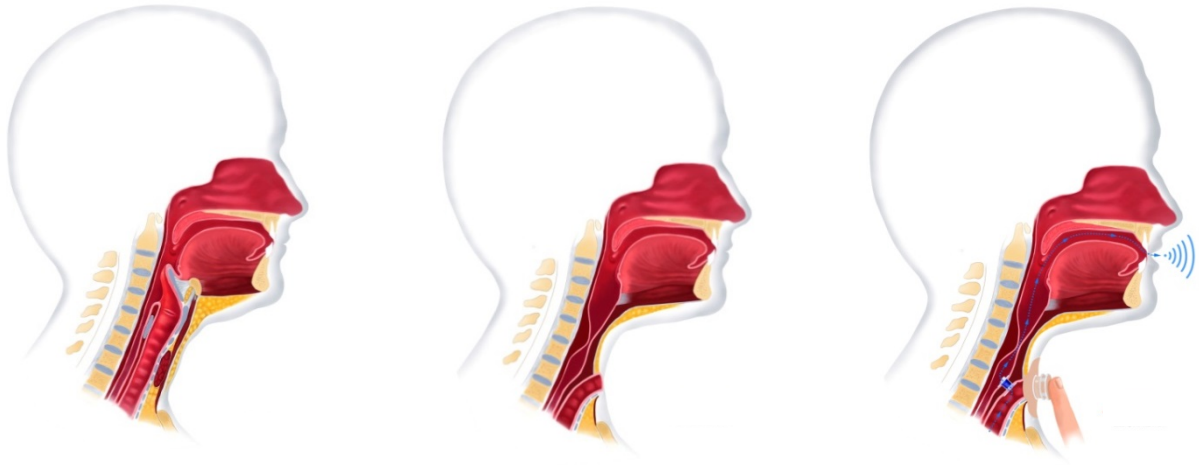

Figure 1 Schematic drawing of normal anatomical situation (left), anatomical situation after total laryngectomy without voice prosthesis placement (middle), and anatomical situation after total laryngectomy with voice prosthesis and heat and moisture exchanger demonstrating tracheoesophageal speech with finger occlusion of the tracheostoma (right).

Thirty-five years ago the very first voice prosthesis for voice rehabilitation after total laryngectomy was described in an article in Polish by Mozolewski[1]. Since then, many efforts have taken place in this area of rehabilitation. In 1980, the first commercially available prosthesis was introduced by Singer and Blom[2]. The first indwelling voice prosthesis (Groningen) was described in 1984[3]. And in 1990, the first Provox® voice prosthesis, manufactured by Atos Medical, was introduced to the market[4, 5], followed by the Provox®2 in 1997[5], the Provox® ActiValve® in 2003[6], and the non-indwelling Provox® NID™ in 2005[7].

In 2009 the Provox® Vega™ with SmartInserter™ was introduced[8]. In 2014 the Provox® Vega™ XtraSeal™ with an extra collar was introduced to reduce leakage around the puncture. The Provox® line of voice prostheses is being used worldwide, which is expressed in many publications in many languages.

This literature review summarizes the published materials about Provox® voice prostheses and focuses on publications that describe its performance in terms of success rates, complications, device life time, and voice and speech.

2 The Provox® voice prostheses product range

The Provox® voice prosthesis is bi-flanged and made of medical grade silicone rubber. The esophageal flange is more rigid than the tracheal flange. The outer diameter is 22.5 French. The prosthesis is available in several lengths. The valve is molded in one piece with the prosthesis and is supported by a fluoroplastic valve seat (blue ring that is tightly secured into the shaft of the prosthesis and that is radiopaque). This first Provox® prosthesis was (re)placed retrograde through the oral cavity by means of a GuideWire, see Figure 2.

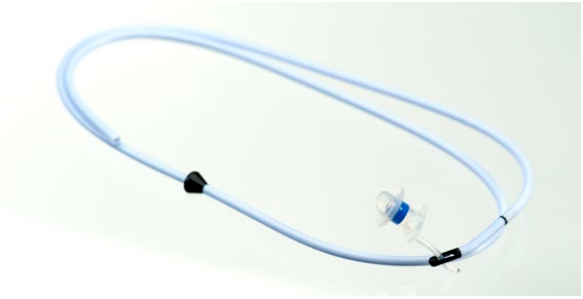

Figure 2 Picture of the first Provox® voice prosthesis with Provox® GuideWire insertion system.

The Provox®2 voice prosthesis is the successor of the Provox® prosthesis, with the main difference being the method of prosthesis placement. While the original Provox® was placed in a retrograde manner through the oral cavity, the Provox®2 prosthesis is placed in anterograde manner through the tracheostoma. The primary placement, after primary or secondary puncture is still performed in retrograde manner using the Provox® GuideWire. To enable anterograde placement, the flanges of the Provox®2 are more flexible than those of the original Provox® prosthesis. The outer diameter is 22.5 French, and the prosthesis is available in the lengths 4.5, 6, 8, 10, 12.5, and 15 mm, see Figure 3.

Figure 3 Picture of the Provox®2 voice prosthesis in various sizes with insertion system.

The Provox® ActiValve® voice prosthesis was developed with the aim of solving problems in a select patient group that is experiencing extremely short device life time due to excessive Candida growth or under-pressure in the esophagus during swallowing or inhalation. The prosthesis is designed with a Candida resistant fluoroplastic valve and valve seat, using magnets available in three different strengths to support valve closure. Outer diameter and available lengths are equal to Provox®2, see Figure 4.

Figure 4 Picture of the Provox® ActiValve® voice prosthesis.

The Provox® NID™ is a non-indwelling voice prosthesis that is developed for replacement by the patient him- or herself. This prosthesis is available in two different diameters (17 Fr and 20 Fr), and in the lengths 6, 8, 10, 12, 14, and 18 mm. The dimensions of the non-indwelling prostheses are different from those of the Provox indwelling prosthesis to match the dimensions of non-indwelling prostheses of other manufacturers and to facilitate self-insertion. The prosthesis is colored blue to enhance visibility for self-replacement and maintenance, see Figure 5.

Figure 5 Picture of the Provox® NID™ voice prosthesis with inserter.

The Provox® Vega™ voice prosthesis with SmartInserter™, introduced in 2009, is the third generation Provox voice prosthesis. The Provox® Vega™ voice prosthesis has similar characteristics and features as the Provox®2 System. The housing and valve flap are molded in silicone rubber and the valve seat is made of fluoroplastic. Unlike the Provox®2 they are not molded in one piece. The valve flap is molded separately and placed inside the fluoroplastic, candida-resistant valve seat. The valve seat is angled and lowered into the shaft. The inner lumen of the Provox® Vega™ voice prostheses is larger, while the outer diameter has remained the same. The Provox® Vega™ voice prostheses are designed to have good airflow characteristics. The flanges are slightly thinner and larger. The tracheal flange is oval, designed to better fit the tracheal anatomy. The safety strap is attached as in Provox® to eliminate interaction with the tracheal mucosa. With the SmartInserter™ insertion system the voice prosthesis is stored in a container inside the inserter. Unlike Provox®2 the clinician does not need to fold the esophageal flange. The flange is folded automatically when the prosthesis is preloaded. The Provox® Vega™ is available in 3 different outer diameters, matching those of the Provox®2 (22.5 Fr) and Provox® NID™ (17 Fr and 20 Fr). Initial placement during surgery is the same as for Provox®.

The Provox® Vega™ voice prosthesis comes pre-loaded inside the Provox® SmartInserter™. It comes with a Provox® Brush for cleaning, see Figure 6.

Figure 6 Pictures of the Provox® Vega™ voice prosthesis with SmartInserter™.

The Provox® Vega™ XtraSeal™ voice prosthesis was introduced in 2014. The Provox® Vega™ XtraSeal™ has similar characteristics and features as the Provox Vega, with an extra collar attached to the esophageal flange. It is intended to help prevent leakage around the prosthesis from the esophagus into the trachea. The Provox® Vega™ XtraSeal™ is inserted as an outpatient procedure with the Provox® SmartInserter™. The

Provox® Vega™ XtraSeal™ is available in various lengths, and in 3 different outer diameters (22.5, 20 and 17 Fr).

Figure 7 Pictures of the Provox® Vega™ XtraSeal™ voice prosthesis

Below, the results of a review of literature for each of the different prostheses are presented, starting with the original Provox® voice prosthesis, and followed by the Provox®2 voice prosthesis, the Provox® ActiValve®, the Provox® NID™ and the Provox® Vega™ with Provox® SmartInserter™.

Although the original Provox® voice prosthesis is currently only used in a small number of patients, and the majority of patients use the Provox®2 voice prosthesis, the results are still considered relevant since the Provox®2 voice prosthesis is based on the original Provox® voice prosthesis. Some studies describe a mixture of Provox® and Provox®2 prostheses, or of different brands of voice prostheses, this is mentioned in the text.

3 The Provox® voice prosthesis

3.1 Device Life, Success Rates, and Complications

The first results with the Provox® voice prosthesis were described by Hilgers and Schouwenburg[4] who reported on 79 laryngectomized patients. Sixty-seven of them used a Groningen prosthesis that was replaced by the new Provox® prosthesis, in nine of them the prosthesis was placed during a secondary puncture, and in 12 the prosthesis was placed at the time of laryngectomy. In vitro and in vivo airflow characteristics were favorable; all 67 patients whom previously used the Groningen prosthesis experienced lower airflow resistance. Ninety-one percent of the patients achieved good voice quality. Eighty percent kept using the prosthesis successfully in the long-term (9% died, 6.7% had the fistula closed, and in 3.5% the correct size was not available during the trial). The mean device life was 154 days. Replacement was successfully carried out in the outpatient setting, but in 3 patients it was complicated due to severe hypopharyngeal stenosis. Complications were short-term enlarged fistula in eight patients (solved with shrinkage of the puncture tract by removing the prosthesis for some days), fistula closure in three patients due to hypertrophic scarring, and fistula closure in three due to intractable leakage around the prosthesis. The prosthesis was easy to maintain.

Balle and Thomsen[9], in a paper in Danish, state that the Provox® voice prosthesis had several advantages over their previously routinely used Bivona Duckbill prosthesis. They found it advantageous that the prosthesis retained well in the fistula, that the lumen was larger, and that the device life was longer (6 to 18 months as compared to 1 to 3 months).

Van Weissenbruch and Albers[10] prospectively studied 37 laryngectomized patients (who used 72 Provox® prostheses) during the period of February 1991 and February 1993. After 1 year, functional TE speech was obtained in 95% of the patients that had received primary puncture, and in 78% that received a secondary puncture. Average device life time was 5.4 months. Complications were leakage through prosthesis (35%), leakage around (11%), granulation (8%), displacement of prosthesis (4%), postoperative fistula (8%), fungal colonization (68%), obstruction valve part (16%), hypopharyngeal stenosis (5%), tracheostoma stenosis (5%), dysphagia (14%), and gastric reflux complaints (5%).

Long-term results with the Provox® prosthesis in 132 patients, showed that the mean and median device life were 235 and 141 days respectively (range 21 days to 1230 days) and that good to fair vocal rehabilitation was achieved in 92% of the patients[11]. The main reason for replacement of the voice prosthesis was leakage through the valve due to improper closure caused by Candida deposits. Cultures of 55 removed prostheses showed that on 89% of the prostheses that were removed for leakage Candida species were detected; other species included proteus mirabilis, streptococci, staphylococci, coliforms, haemophilus, klebsiella, pseudomonas, and enterobacter. Complications were widening of the fistula in 20.5% (27 patients), solved by removal of prosthesis for one episode in 15 patients, two episodes in 7, and 3 episodes in one. In 4 patients (3%) the leakage was intractable and the puncture was closed surgically. Other complications leading to (surgical or spontaneous) fistula closure were hypertrophic scarring, prolapse and/or infection of the puncture (4.5%), spontaneous extrusion of the prosthesis (4.5%), postoperative wound infection around the stoma (1.5%), severe hypopharyngeal stenosis (1.5%), and too high or too low position of the puncture (4.5%). None of the complications were associated with irradiation. The mean device life was significantly longer in the patient group with laryngeal cancer (7.4 months) compared to the patients with hypopharyngeal cancer (4.3 months). Radiotherapy also seemed to have an influence on device life, although not statistically significant, device life was longest in non-irradiated patients (9.6 months), and longer in patients who had undergone pre-operative radiation (6.1 months) than those who had had postoperative radiation (5.8 months).

A 6-year retrospective review from the UK (1986-1990) of different types of indwelling voice prostheses (Groningen High Resistance (N=83), Groningen Low Resistance (N=71), and Provox® (N=16) showed that there was no statistically significant difference in the in situ device life time for the devices. They also found that with the Groningen prostheses relatively more valves were replaced for increased speaking resistance than with the Provox® prosthesis[12].

Callanan et al.[13], reported about a cohort of 28 patients using the Provox® voice prosthesis, the average device life was 148 days (median 120 days). Speech intelligibility was found to be good and no major surgical complications were associated with valve insertion or use. Two patients needed downsizing due to leakage around with a too long prosthesis, three patients showed migration of the esophageal mucosa around the valve housing which was solved by inserting a longer prosthesis, one patient ingested the prosthesis.

Van den Hoogen et al.[14] prospectively compared the Provox® voice prosthesis with the Groningen and Nijdam prosthesis. 845 consecutive replacements (prostheses were placed at random) were evaluated in 158 patients. The replacement indications for the prostheses differed; the Provox® was more often replaced for leakage, whereas the Groningen and Nijdam were more often replaced for increased speaking resistance. Although the average device life of the Nijdam prosthesis was longer (19 weeks) than that of the Provox® (13 weeks) and Groningen (15.8 weeks), there were other prosthesis-related issues with the Nijdam prosthesis that warranted replacement by another type of prosthesis. Granulation tissue and hypertrophic scar tissue formation were the most frequent complications.

Toma et al.[15] describe their results with the Provox® prosthesis in a cohort of 31 patients. Long-term success rate was 88%. Average device life was 148 days. Complications were inferolateral migration of the fistula in one patient, migration of esophageal mucosa around the valve in three, and prosthesis ingestion in one.

Ollas et al.[16] (article in Portuguese) retrospectively studied 101 laryngectomized patients using voice prostheses (95 Provox®, 4 Blom-Singer, 2 Groningen). The median device life was 327 days. In general, the first prosthesis lasted longer than the subsequent ones. At the end of the study, of the 101 patients, 12 had died, 8 were lost to follow-up, 20 had their puncture surgically or spontaneously closed for a variety of reasons (ingestion (2), fistula (6), prefer esophageal speech (3), stenosis (2), extrusion (1), not motivated (4), unknown (2)). Of the remaining 63 patients, 95% had a fluent voice and average device life was 322 days.

Slavicek et al.[17] (article in Polish) describe the results of 53 patients (273 prostheses) using a Provox® voice prosthesis. All were placed during a secondary puncture procedure. Over 85% of the patients were able to produce satisfactory voice. Median device life was 98 days. Local inflammation or reaction occurred in 28.1%, resulting in removal or extrusion of the prosthesis in 14.2%.

Laccourreye et al.[18] (retrospective study Nov 1990-June 1994; 37 patients (100 Provox® prostheses) observed an average device life time of 311 days (including replacement for salivary leakage through (33%), salivary leakage around (27%) , deterioration of the prosthesis (24%), and increased airflow resistance with excessive crusting (16%). One early case of cellulites was seen and treated with antibiotics, late complications were uncommon and included granulation tissue formation treated with CO2 laser or electric cautery (6), tracheostoma stenosis (3), tracheoesophageal puncture necrosis due to ill-fitting voice prosthesis treated with insertion of a small diameter catheter and reinsertion of well fitted prosthesis (1), cervical cellulites (1), and swallowing impairment (1). No statistical relation was noted between the various complications and the in situ life time of the prosthesis.

In UK, De Carpentier et al.[19] retrospectively studied the device life time in 39 patients using 81 Provox® prostheses. Valve failure was determined as leakage around, though, or inability to produce voice. Median device life was 4.5 months. More detailed investigation showed that a small group of patients (7.7%) accounted for a substantial part of the replacements (24.7%) No particular patterns or conditions could be identified for this subgroup. The lifetime of the first valve was negatively affected by previous radiotherapy, subsequent prosthesis failures were neither affected by previous radiotherapy, nor by the length of previous prosthesis lifetimes.

A comparison between the Provox® and Blom-Singer indwelling voice prosthesis (article in Italian) showed that the average device life of the Provox® was 6 months (ranging from 2 to 18 months) and the average device life of the Blom-Singer was 5 months (range 3 to 15 months)[20]. This study was done in 30 patients, 16 received a Provox® and 14 a Blom-Singer, all punctures were made secondarily; the Provox® prosthesis was placed immediately and for the Blom-Singer prostheses first a catheter was placed and the prosthesis two days later. The Provox® patients were hospitalized 24 hours and the Blom-Singer patients 72 hrs. The overall success rate was 96%. Complications were pooled for both types of prostheses and included fistula dilation in 10%, cellulites in 6.6%, candida growth on prosthesis in 26.6%, and extrusion in 6.6%.

De Racourt et al.[21] (article in French) reported on voice rehabilitation in 62 laryngectomized patients, all with a 5 year follow-up, treated between December 1987 and February 1998. The prostheses used in these patients were Herrman (until 1993), Provox® (majority, but no specific numbers given), Traissac and Blom-Singer. Complications were pooled for all prostheses and were secondary pharyngostoma (1), pharyngeal stenosis (2), tracheostoma stenosis (3), enlarged fistula (16 patients, 37 episodes of which 28 were treated with shrinkage by placement of a narrow catheter, 2 healed spontaneously, 7 were surgically closed of which 4 were repunctured later).

Seventeen patients had the prosthesis permanently removed, 4 because of complications, 9 due to absence of motivation, 3 due to poor voice, 1 due to cancer recurrence.

Aust and McAffrey[22], in a retrospective study of 21 patients, found an average device life time of 166 days (24 replacements in 13 patients; leakage through as the cause in 3 valve changes and leakage around due to incorrect size in 21 changes). Success rate was 88% and complications were partial retraction of prosthesis into esophagus due to placement of too short prosthesis in 2 patients, granulation tissue in one, and cellulites in one.

Nasser et al.[23] (article in French) in a prospective study carried out from March 1994 until September 1996, report on 52 patients using Provox® voice prostheses. Device life time varied from 2 – 19 months, with an average of about 8 months. Complications were leakage around (9 events), obstruction (30 events), and migration of prosthesis (17 events). Seventy-seven% of the patients had good or excellent speech.

A prospective randomized controlled study compared the Provox® voice prosthesis to the Blom-Singer indwelling voice prosthesis[24]. Comparisons were made for device life and voice parameters. Fifty-two patients were randomly selected to receive Blom-Singer or Provox® and 113 prostheses were placed in total. Voice quality was overall good and comparable for both types of prostheses. Both prostheses lasted about 4 months (median 14.5 weeks for Provox® and 15 weeks for Blom-Singer).

Baumann et al.[25] in an article in German used the HRS (Harrison & Schultz) scale that judges voice quality, use of the prosthesis, and prosthesis care as criteria to report the success of tracheoesophageal speech. According to these criteria, 44% of the patients acquired successful voice rehabilitation (defined as 12-15 points on this scale). They further showed that the successful users needed more frequent replacements of their prostheses (average device life 3.9 months) than the unsuccessful users (average device life 5.6 months). Complications occurred in 26 out of the 478 prostheses replacements: esophageal mucosal overgrowth/covering (14), prosthesis aspiration or ingestion (3), local infection (4), aspiration pneumonia (3), and granulation (2).

Biacabe et al.[26] retrospectively studied device life time and compared cost of replacement for general or local anaesthesia, they report an average device life time of 241 days.

Cornu et al.[27], reported on the results of voice rehabilitation using the Provox® voice prosthesis in South Africa. A cohort of 128 patients, laryngectomized between 1995 and 1998 was studied. Average device life was 303 days. Complications (22 adverse events in 16 patients) were posterior displacement of the prosthesis (5), anterior displacement of prosthesis (9 events), granuloma formation (2 events), enlarged fistula (3 events), and leakage adjacent to the fistula (3 events).

Gultekin et al.[28] studied the effects of neck dissection and radiotherapy on short-term speech success. Thirty-two male patients treated for laryngeal squamous cell carcinoma were included. Nine patients underwent total laryngectomy and 23 underwent total laryngectomy combined with neck dissection, and 17 of the 23 with neck dissection were managed with postoperative radiotherapy. No complications were noted with intraoperative prosthesis placement. No prostheses were dislodged in the postoperative period. Authors conclude that neck dissection and postoperative radiotherapy have no significant influence on short-term speech success in VP restoration patients.

In a retrospective study by Cocuzza et al. 2014[29], 61 laryngectomized patients were analyzed for the occurrence of puncture related problems. Patients who received postoperative radiotherapy were compared with those patients that did not. All patients included in the study had known gastroesophageal reflux disease. Results showed a greater incidence of puncture related problems in the group of patients who had undergone post-operative radiotherapy (45%) compared with patients who did not (17%) although all patients were treated with PPI's.

Imre et al.[30] conducted a retrospective study between 2006 and 2011 of 47 male laryngectomized patients fitted with Provox® indwelling voice prosthesis. Results showed that the overall complication rate was 42.6% during mean follow-up of 15.3 months. Tracheoesophageal puncture enlargement (n=9, 19.1%) was the most common minor complication and the most common cause of complete closure of TEP in this study.

Chaturvedi P, et al 2014[31] conducted a pilot study of 58 laryngectomized patients who developed prosthesis dysfunction. Prosthesis lifespan and probable factors affecting it were analyzed. Central leak was found in 43%, peri-prosthetic leakage occurred in 57% and was the most common reason for prosthesis replacement. Mean device lifespan was 18 months and significant correlations were found between the prosthesis lifespan and the consumption of curd, and between lifespan and history of prior radiation.

Yenigun et al. 2015[32] assessed the factors that influence the longevity and replacement frequency of Provox® voice prostheses. The records of 27 patients, attending follow-up between 1998 and 2012 were retrospectively reviewed. The success rate was 85%. The average lifespan of the prosthesis was 17.1 months (range 1-36 months). A strong correlation was found between life time of the prosthesis and postoperative follow-up duration. No correlation was found between prosthesis life time and purpose of placement (primary or secondary puncture), reflux history, antifungal use or presence of leakage. The authors recommend frequent patient control visits, proper patient selection and regular prosthesis care to prolong the life time of the voice prosthesis.

Serra et al. 2015[33] reported their 15-year experience with Provox voice prosthesis. A retrospective clinical analysis was carried out in 95 patients between 1998 and 2013. The overall success rate was 87.5%, 84% in primary TEP and 91% in secondary TEP. The median device lifetimes were 150 days (range 120-180) for Provox®1, 125 days (range 95-155) for Provox®2, and 140 days (range 125-165) for Provox® Vega™. Overall complication rate was 13%, of which 90% pharyngocutaneous fistula, 5% bleeding and 5% other medical complications. Trachea-oesophageal voice failure was recorded in 6% (n=6) of the patients, surgical closure was performed: 2% persistent leakage around the prosthesis, 2% giant trachea-oesophageal granuloma, 1% downward fistula migration, 1 patient with persistent poor vocal quality preferring prosthesis removal.

Thylur et al. 2016[34] conducted a retrospective study of 21 patients with 181 device replacements, comparing the device life of Provox®2 and Provox® Vega™. The mean device life for Provox®2 was 115.6 days (median 110 days), and 65.1 days (median 80 days) for Provox® Vega™. A prospective study is planned to evaluate interactions of diet and microflora on biofilm formation to potentially explain difference lifetime between Provox®2 and Provox® Vega™.

In a retrospective observational study by Lewin et al. 2017[35], the device life of voice prosthesis was reexamined. In total 3648 voice prosthesis (VP) were placed in 390 patients between July 2003 and December 2013. In 69.4% the voice prosthesis was replaced because of leakage through. Median (range) device life was 61 (1-816) days for all prosthesis. Indwelling VPs had significantly longer device life than non-indwelling (70 days vs 38 days). The VP with the longest life was the Provox® ActiValve® with a median of 161

days. Neither radiation therapy nor extent of surgery had a meaningful impact on device life. The overall VP device life is lower than historically reported. This might be explained by the medically and socially complex population as a consequence of the effect of organ preservation treatment protocols.

3.2 Quality of Life studies

Quality of life (QOL) is an important health domain to consider when evaluating the success of surgical voice restoration. Polat B, et al 2015[36], found that patients who underwent total laryngectomy had seriously reduced QOL and self-esteem. In an uncontrolled single-arm study they compared patients' (n=30) psychosocial statuses pre- and post-voice prosthesis insertion (Provox®). Results indicated that placement of a voice prosthesis improved quality of life, self-esteem, and sexual function ($p < 0.05$). Additionally, symptoms of depression and anxiety decreased ($p < 0.05$).

3.3 Aerodynamic Characteristics – Phonatory Effort

In vitro studies of the aerodynamic characteristics of the Provox® voice prosthesis at increasing airflows (0.05 – 0.4 l/s) showed that the opening pressures of the Provox® voice prosthesis are considerably lower than those of the Groningen Standard, Groningen low-resistance and Blom-Singer Duckbill prosthesis[37]. The Blom-Singer low pressure prosthesis shows lower opening pressures than the Provox® voice prosthesis in the low airflow range, but higher opening pressures in the high-airflow and speaking range[38]. Although the voice prosthesis is only responsible for part of the total resistance (the neoglottis is responsible for the other part), favorable airflow characteristics are expected to enable the laryngectomized patient to speak with less effort, which is indeed confirmed by the fact that patients who changed from the Groningen prosthesis to the Provox® prosthesis experienced less effortful speech[4].

Chung et al.[39] compared the aerodynamic performance of the Provox® and Groningen low resistance voice prosthesis both in vitro and in vivo and their aerodynamic measurements showed that the Provox® voice prosthesis has a lower airflow resistance. The median intra-tracheal phonatory pressure for phonation at 75dB was significantly lower (2.1kPa) in patients using the Provox® voice prosthesis. Although speech rate, maximal phonation time, and maximal vocal intensity showed no significant difference, the intelligibility of speech in noise produced with the Provox® was significantly better than the speech produced with the Groningen LR voice prosthesis. Subjectively, most patients preferred the Provox® prosthesis because speech required less effort. Miani et al.[40] et al compared the in vitro and in vivo aerodynamic performance of the Provox® prosthesis with the Staffieri prosthesis and found that the aerodynamics of the Provox® prosthesis were significantly better, both in vitro and at high speaking intensities also in vivo. Belforte et al.[41] confirmed the favorable in vitro airflow characteristics of the Provox® prosthesis in comparison with the Staffieri, Groningen Standard, Groningen Low Resistance and Panje voice prosthesis.

Van den Hoogen et al.[42] prospectively studied speech and voice rehabilitation (phonatory skills, speech quality, voice quality, stoma technique) with the Groningen LR, Nijdam, and Provox® prostheses and found no statistically significant differences between the different types of prostheses.

3.4 Success after Extensive Reconstruction

Panarese et al. [43] have described the use of the Provox® prosthesis in patients after pharyngolaryngectomy with jejunum transplant reconstruction. Six out of nine patients developed a successful voice with the jejunum transplant and Provox® voice prosthesis. Two patients who originally had received a Blom-Singer prosthesis expressed their preference for the Provox® voice prosthesis as they thought it provided a better voice. Hilgers et al.[44] also showed that in patients with extensive pharyngeal resection and reconstruction, voice rehabilitation with the Provox® was successful in the majority of patients, although voice quality was sometimes of poor quality due to the nature of the reconstruction. Baijens et al.[45] describe a case-study in which a patient after a circumferential pharyngolaryngectomy and neopharyngeal reconstruction with a jejunal free flap is presented. This case demonstrates that after extensive laryngopharyngectomy with jejunal free flap reconstruction, a tailored rehabilitation program can improve voice and swallowing function.

3.5 Quality of Speech

A study regarding speech quality showed that speech quality with the Provox® voice prosthesis in comparison with the Groningen High Resistance and Groningen Low resistance was good, there was a trend for the Provox® voice prosthesis to produce the best scores[46]. The intelligibility of speech in noise produced with the Provox® was found to be significantly better than the intelligibility of speech produced with the Groningen LR voice prosthesis[39].

A prospective nonrandomized cross-sectional study by Dabholkar JP et al 2015[47] evaluated voice quality in thirty patients with Provox® voice prostheses. Voice quality measures were taken immediately postoperatively and at 6-month and 1-year intervals using the parameters of functional outcomes GRBAS scale, maximal phonatory duration (MPD), and words per breath (WPB). All patients had good voice results at the end of 1 year after Provox® insertion with voice quality results improving with time.

3.6 Microbiological Studies

A microbiological study of 37 Provox® voice prostheses that were removed for leakage or increased phonation pressure (average device life 24.5 weeks, range 8.5 – 61.2 weeks) showed that valve destruction was mainly caused by Candida colonization, although also other upper respiratory tract commensals such as Staphylococcus Aureus, were also found[48]. Mycological and scanning electroscopic assessment of three Provox® prostheses removed for failure demonstrated that the Candida mycelium on these prostheses was a surface colony rather than growing into the valve substance, suggesting it might be feasible to control its growth by mechanical cleansing or the use of topical antifungal agents[49].

3.7 Accessories

In addition to the Provox® voice prosthesis, a surgical TE puncture system consisting of a Pharynx protector, Cannula, and Trocar, a cleaning Brush, and a Plug to temporarily prevent leakage through the prosthesis were developed[11]. Padhya et al.[50] describe an alternative approach for secondary tracheoesophageal puncture in the difficult laryngectomy neck, using the Provox® trocar.

4 The Provox®2 voice prosthesis

4.1 Device Life, Success Rates, and Complications

In 1997 the Provox®2 voice prosthesis was introduced to the market and the first clinical results in 44 patients were described by Hilgers et al.[5] The Provox®2 voice prosthesis is quite similar to the Provox® voice prosthesis but it was adapted (more flexible flanges) to enable anterograde insertion through the tracheostoma, instead of retrograde through the mouth and throat. The anterograde replacement was seen as a large benefit by the patients, 91% did not find the replacement uncomfortable at all, and 9% found it slightly uncomfortable. This was a large improvement, since only 40% of these patients found the anterograde replacement not uncomfortable, while 30% found it slightly uncomfortable and the remaining 30% found it quite to very uncomfortable. 18% of the patients admitted that they delayed replacement of a leaking prosthesis because they found the replacement uncomfortable, on average about 3 weeks. The pull-out force was on average 7.9 N.

Koscielny and Bräuer[51] compared the replacement systems of Provox® and Provox®2 in 45 laryngectomized patients. A total of 177 changing procedures was carried out, 69 with the retrograde Provox® system and 108 with the anterograde Provox®2 system. The Provox® could be changed without problems in 68% of the cases and the Provox®2 in 94% of the cases. On average the device life time of the prostheses was 6 months and there was no difference in durability between Provox® and Provox®2. Patient interviews revealed that most patients preferred the Provox®2 changing procedure.

Graville et al. who described results of both the Provox®2 prosthesis and the Blom-Singer Indwelling found that leakage through the device secondary to yeast colonization occurred with equal frequency in the Blom-Singer and Provox®2 prosthesis[52].

In a prospective multi-institutional assessment of the Provox®2 voice prosthesis in four institutions, 239 consecutive laryngectomized patients received a Provox®2 voice prosthesis[53]. Results of this study showed that anterograde insertion was always successful, 97.1% of physicians preferred the anterograde method and 93.7% of patients did. The device lifetime of the Provox®2 voice prosthesis was shorter than Provox® (median of 125.5 days versus 104 days), but this difference was not statistically significant. The authors explain that this difference is most likely due to a patient-delay: the average reported patient-delay to have a leaking Provox® prosthesis replaced was 18.9 days on average.

In a large retrospective study (Nov 1988-May 1999, 318 patients, 2700 prosthesis replacements) of both the Provox® and Provox®2 voice prosthesis, 95% of patients were successful long-term users of whom 88% had a fair to excellent voice quality[54]. This study showed also that the device life of the Provox®2 prosthesis was shorter than that of the Provox® (median 120 versus 92 days). The first prosthesis, placed at the time of surgery lasted significantly longer than subsequent prostheses. Significant clinical factors for increased device life time were no radiotherapy and age over 70 years. Most prostheses were replaced for leakage through the device (73%). Complications were leakage around the prosthesis (13% of replacements; in 10% solved by downsizing and in 3% requiring further treatments such as temporary shrinkage of fistula), and hypertrophy/infection of the puncture (7% of replacements).

Balle et al.[55] report on 10 years of experience with voice prostheses in a total of 88 patients. During the first two years non-indwelling Blom-Singer Duckbill prostheses were used and in the later years Provox® and Provox®2. The patients on the Duckbill prostheses were converted to Provox® prostheses (the authors report they preferred the Provox®

prosthesis due to its low opening pressure, and its hygienic handling, and because it is well tolerated by the patient and the device life is fairly long). The average device life for Provox® was 3.1 months and the average device life for Provox®2 2.3 months. The authors suspect that the shorter device life of Provox®2 in their study may be related to uncareful insertion. Their complications were granulation tissue (in 14 patients) and infection (in 5 patients).

Lequeux et al.[56] also found the device life of Provox® (N=24) to be longer than that of Provox®2 (N=128)(median 303 days versus median 144 days). These authors believe that the difference in elasticity between the two valves could explain the difference in device life.

Ahmad et al.[57] report results of a retrospective study of 100 patients over a 10 year period (1989-1999). They started with non-indwelling Blom-Singer valves and converted them to Provox® when it became available. Most patients were converted at their own request due to improved voice quality and easier maintenance. When Provox®2 became available patients were converted to Provox®2 because of a marked patient preference for the ease and convenience during valve change. Eighty-two percent of the patients achieved average to good speech. A German retrospective study in 58 laryngectomized patients treated over a 6 year period (1993 -1999) analyzed the device life of a total of 378 prostheses (136 Provox®, 78 Provox®2, 172 Blom-Singer)[58]. The average device life was 244 days for Provox®, 96 days for Provox®2, and 107 days for Blom-Singer. The device life of the Provox® was significantly longer than that of the other ones, but the authors state that as they are more difficult to handle they are not considered for routine use. The device lives for Provox®2 and Blom-Singer were not significantly different.

Hotz et al.[59] describe the results of a retrospective study over a 6 year period (1992-1998) in 82 patients. Both Provox® (initially) and Provox®2 were used. They separate the postoperative follow up in 3 phases; I) 0-9 months, II) 10-30 months, and III) 31- 72 months and determine success based on the HRS scale (quality, use, and care; 12-15 points is considered a success). In phase I device life was longer in the successful users (4.2 months versus 3.9 months) and in Phase II it was the opposite: the unsuccessful users experienced longer device lives. Complications were scarce; aspiration (1), ingestion (2), aspiration pneumonia due to periprosthetic leakage (3), peristomal infection (4), granulation (2). Periprosthetic leakage was seen more often in the old Provox® prosthesis. In 14 patients the fistula closed spontaneously, 6 of those patients did not use their prosthesis.

Fajdiga et al.[60] report on two different speaker groups; esophageal speakers (35) and tracheoesophageal speakers (32) who attended speech therapy between 1998 and 2002. The tracheoesophageal speakers used Provox® and Provox®2 voice prostheses, and had initially also used another type of prosthesis (not reported which one). Results for all prostheses are pooled (including the initially used unknown type of prosthesis). Average device life time was 5.5 months. Complications were inflammation (12 events in 5 patients), leakage around requiring replacement of prosthesis (19 events in 7 patients), leakage through prosthesis (valve failure) requiring replacement of prosthesis (32 events in 14 patients), leakage through prosthesis (yeast colonization, increased resistance) (160 events in 32 patients), and prosthesis aspiration (4 events in 4 patients).

Trussart et al.[61] retrospectively studied long-term follow-up results (3 to 16 yrs) in 35 patients using 178 prostheses. The average lifespan was 165.5 for the Provox® (N=93), 143.5 for Blom-Singer (N=73), 135 for Groningen (N=5), and 195 days for VoiceMaster (N=7). Complications were pooled for all prostheses and consisted of 12 cases of periprosthetic leakage (6.74%) treated with collagen injection (11) and silastic at tracheal end of prosthesis (1), 31 granulomas (17.4%) treated with CO2laser evaporation (25) or

silver nitrate cauterization (8), 3 partial stenoses of the puncture tract (1.6%) treated with CO2 laser under general anesthesia, and one temporarily removed prosthesis (0.5%).

Makitie et al.[62] report on a retrospective review of the records of 95 laryngectomies performed over a 10-year period. They performed voice rehabilitation using a Provox® or a Provox®2 voice prosthesis. The average device life was 10 months. The complication rate was low; the authors stress the importance of a multidisciplinary approach. Complications were (% of the total number of replacements): leakage through the prosthesis 51.8%, obstruction of the prosthesis 14.2%, inadequate size of prosthesis 12.4%, granulation tissue in fistula 9.2%, leakage around prosthesis 7.3%, puncture too high or low 4.1%, extrusion of prosthesis 0.5%, stricture of tracheostoma 0.5%. 78% of the patients had average to good voice quality.

Device life time often differs from country to country. This is thought to be caused by dietary differences, while also economical/healthcare reimbursement difference may play a role. A study in Turkey, including 50 patients using 62 voice prostheses, found an average device life time of 24 months[63]. Morshed et al.[64] (article in Polish) present the results of 2 years of using the Provox®2 voice prosthesis in 21 patients. In 7 patients the device was replaced and device related lifetime was 216 days on average. In non-radiated patients the average was 215 days and in radiated patients it was 150 days.

Lam et al.[65] report on 60 patients operated upon between 1998 and 2004. A total of 203 prostheses were used (192 Provox®, 7 Blom-Singer Indwelling, 3 Blom-Singer Duckbill, 1 VoiceMaster). The median device lifetime for the indwelling prostheses was 8.2 months. Device life time was longer in patients under the age of 60 (9.2) than in those over 60 (6.5 months). The prostheses were placed at the time of surgery. The device life of the first voice prosthesis was longer than that of the subsequent ones (9.6 months). Complications were pooled for all types of prostheses used and were: persistent tracheoesophageal fistula leakage in 3 patients, frequent valve changes in one patient, extrusion of prosthesis leading to spontaneous fistula closure in 2 patients, and parastomal tumor recurrence leading to prosthesis removal in two patients.

Bien and Okla[66] (article in Polish) retrospectively studied device life and complications in a group of 106 laryngectomized patients (132 prostheses replacements; included between 2002 and 2004). In 68.9% (73 patients) the prosthesis was placed primarily and in 31.1% (33 patients) secondarily. The average device life time was 9.8 months in radiated patients and 9.7 months in non-radiated patients. The most common complications were infection after secondary puncture with placement of the prosthesis (12.1%) and partial extrusion with closure of the puncture tract (7.5%).

Calder et al.[67] retrospectively studied complication rate, hospital admissions and need for further surgery in patients fitted with voice prostheses (Provox®, Provox®2, Blom-Singer) in 99 patients undergoing a total laryngectomy over a 10-year period (1993-2002). The overall complication rate was 45%, granulation tissue formation around the prosthesis was the most common complication (20%). However, the authors state that the data for their study were incomplete, date of valve change, type of valve use and reasons for change were often not recorded. This was treated with silver nitrate cautery or temporary removal of the prosthesis and insertion of a small diameter catheter.

Unlike in many other countries, in Japan, esophageal speech is still considered the first choice for voice rehabilitation. Prosthetic speech is seen as an alternative when the speaker does not succeed at esophageal speech. Yamada et al.[68] reported on the success of the Provox®2 voice prosthesis secondarily inserted in 13 unsuccessful esophageal speakers and 2 successful esophageal speakers who requested a voice prosthesis. Voice rehabilitation was successful in 13 patients; in one patient the prosthesis

was removed due to tracheostomal stenosis and in one because of esophageal stenosis. Terada et al.[69], in the largest study on voice prosthesis in Japanese literature, reports on 32 patients (30 secondary punctures) who received a Provox®2 voice prosthesis between Sept 2000 and Dec 2004. The success rate was 90.6%. The average device life in laryngeal carcinoma patients was 27.2 weeks and in hypopharynx carcinoma patients it was 16.6 weeks, for the total group it was 21 weeks on average. Early complications were severe oedema or necrosis around the puncture in three patients (one resolved with temporary insertion of small diameter catheter, two resolved with conservative treatment). Late complications were granulation tissue formation (3), aspiration pneumonia (2), salivary leakage around prosthesis (1), dropping of cleaning brush in trachea – retrieved with forceps (1).

Kummer et al.[70] carried out a retrospective study of 145 laryngectomized patients who had undergone prosthetic (Provox® and Provox®2) voice restoration between 1990 and 2002. They compared success rates and complications between the patients who had received radiotherapy period to their total laryngectomy (N=17) and those who did not (N=128). Results showed that previous radiation decreased the rate of success and increased complications. The risk of the fistula related complications aspiration around the prosthesis, widening of the shunt, esophageal or tracheal dislocation of the prosthesis, and spontaneous or surgical closure all increased with previous radiation.

González Poggioli et al.[71] retrospectively analyzed their experience with voice prostheses in 96 laryngectomized patients treated between Oct 2000 and Dec 2005. The prostheses used were Provox®2 (81), Blom-Singer (7), Herrmann (7), and Groningen (1). 74% of the patients used the prosthesis as their usual means of communication. They found no significant difference between the prosthesis used and achieving satisfactory phonation. Average device life (pooled for all prostheses) was 9 months. Twenty-one prostheses were removed, the majority for lack of use or failure to use. This could be due to a lack of support, the authors' state that the support from a speech therapist is important (in Spain this is not yet common practice).

Elving et al.[72] investigated the influence of radiotherapy on device life of Provox®2 and Groningen Low Resistance voice prostheses. All patients primarily received a Groningen LR voice prosthesis and subsequent prostheses were either Provox®2 or Groningen (and a small number of Provox® that was left out of further analyses). The average device life time of the first Groningen prosthesis used immediately after surgery was 180 days and of subsequent ones the average was 137 days. The average device life time of Provox®2 was 90 days. The difference in device life time between Provox®2 and Groningen was not significantly different. The study identified an association between radiation on the primary tumor site with a dose equal to or more than 60Gy and limited life time of voice prostheses.

Ozkul et al.[73] report on intelligibility and device life time of voice prosthesis (204 Provox®2, 17 Blom-Singer, 5 Groningen, 5 Turvox) over a 10 year period. Intelligibility was investigated using mono- and double-syllable words. Intelligibility with the Provox®2 prosthesis was 72% for mono-syllabic words and 92% for double-syllabic words, percentages for Blom-Singer were 53% and 77%, for Groningen 52% and 75%, and for Turvox 67% and 87%. Average device life was 18 months for Provox and 5 months for the others. All patients were on a daily intake regime of Turkish yoghurt and kephir which the authors believe to contribute to their low incidence of fungal colonization. Complications are reported to be limited to granulations, aspiration/extrusion, and overgrowth of esophageal mucosa, but no exact figures are given.

Bilewicz et al.[74] report on 39 tracheoesophageal speakers using a Provox®2 voice prosthesis found that 90% of the patients were able to learn tracheoesophageal speech. The mean device life time was 295 days. The most common cause for replacement was leakage associated with mycosis infection (Candida) in 26 cases. Complications were infection of the fistula during radiotherapy (N=7) and widening of the fistula (N=4).

Boscolo-Rizzo et al.[75] retrospectively reported on the results of voice restoration in 75 patients with primary TEP and 18 with secondary TEP. Patients were rehabilitated with indwelling Blom-Singer prostheses until September 2001 and then with Provox®2 prostheses. Overall success rate according to the HRS scale was 81.7%. There was no significant difference in success rate between primary and secondary puncture and there was no difference in surgical complications between primary and secondary puncture.

Ramalingam et al.[76] prospectively compared the Provox®2 voice prosthesis with the Blom-Singer low pressure voice prosthesis for voice, complications and device life. Twenty patients received the Blom-Singer prosthesis and 21 received the Provox®2. Speech quality assessment revealed a better quality of voice production in the Provox®2 voice prosthesis. Patient compliance in valve maintenance was better with Provox®2. Prosthesis related problems like granuloma formation, leakage, candida growth over the valves and prosthetic decay were significantly less in the patients fitted with a Provox® valve. Dislodgement of the prosthesis with closure of the tract, persistent fistula formation, and creation of false passage while reinserting the prosthesis were problems that were encountered with the Blom-Singer prosthesis only. The average device life of the Blom-Singer low pressure prosthesis was 3 months and that of the Provox®2 was 15 months.

Boscolo-Rizzo et al.[77] found that device life time of the prosthesis is significantly influenced by radiotherapy and GERD. The mean in situ device life was 163.3 days in irradiated and 202.9 days in radiated patients. The mean in situ device life was 126.5 days in patients with and 215.7 days in patients without endoscopic evidence of erosive ulcerative gastroesophageal reflux disease (GERD).

Tammam and Ahmed[78] noted in a retrospective study of 5 patients that device life ranged from 5 to 60 months with an average of 24.5 months.

In a retrospective study by Bozec et al.[79] of 87 patients, successful voice rehabilitation was obtained in 82% of the cases. The mean device lifetimes were 7.6 and 3.7 months for Provox® and Provox®2 speech valves, respectively.

Mastronikolis reported an 80% success rate in 12 Provox®2 users in Greece[80].

In a prospective study (2 years), Reumuller et al.[81] investigated shunt-related and device-related complications, device life and microbial colonization in patients with jejunal autograft reconstruction (9), and a standard total laryngectomy (14). No difference in device life was found (reconstruction group mean 116 days, SD±114; TL group mean 129 days, SD±99). Similar complications and reasons for replacement were found. The authors conclude that voice prostheses can be safely used in each group.

Wierzchowska & Burduk[82] published in 2011 on the early and late complications after insertion of the Provox®2 in 76 patients. Late complications were more frequent, with leakage through and leakage around the prosthesis being the most common complications. Authors conclude that this can often be solved by changing the prosthesis, which should be taken into account by medical insurance companies

Issing et al.[83], retrospectively comparing the Provox® with the Eska-Herrmann prosthesis with respect to leakage around (103 patients treated between 1989 and 1998) state that most of their patients experienced salivary leakage at some point in time that was solved by removal of the prosthesis to let the puncture shrink (Eska-Herrmann) or by exchanging the prosthesis Provox®2. The author's further state that their data may be incomplete and (despite the fact that they find no significant difference) they presume that the incidence of leakage around is higher in Provox®2 prostheses. They report the device life of Provox to be 4 to 6 months. No device life data for the Eska-Herrmann prosthesis are provided.

In an Albanian study, Boci et al.[84] analyzed in 2012 the device lifetime of the Provox®2 and found a median lifetime of 279 days (range: 184-995).

In a retrospective study in 91 patients, with 71 secondary insertions and 20 primary insertions, voice rehabilitation was successful in 75.8% of the patients in a study by Lukinovic et al.[85]. Early complication rate was 4.4%, and 10.9% of patients had late complications, with leakage being the most common problem. No significant differences were found for the complications rate and success rate of rehabilitation between groups of patients, formed according to age, irradiation status and timing of prosthesis insertion.

Zimmer-Nowicka & Morawiec-Sztandera analyzed 184 replacements of the Provox®2 in 42 Polish patients. Mean time between replacements was 260 ± 150 days. Most frequent indications for replacement were leakage of fluids through the prosthesis, phonation problems caused by mucosal overgrowth around the prosthesis, inaccurate sizing, deformation, and spontaneous extrusion. The device life of voice prostheses correlated positively with patients' age[86].

In a Turkish study, Kılıç et al 2014[87] evaluated replacements of the Provox®2 in 210 patients (180 males, 30 females). The mean device life time was 7.5 months (range 1 to 48 months). Fungal colonization was detected in 141 patients (66%), granulation tissue developed in 30 patients (14%), 3 patients (1%) swallowed their voice prosthesis, enlarged tracheoesophageal fistula was noted in 2 patients and mediastinitis occurred in one patient (1%). Messing et al. 2015[88] in a US study, found median lifetime of the Provox®2 across 15 patients was 92 days.

In a retrospective study in 41 Provox®2 patients who were rehabilitated between 1997 and 2015, Friedlander et al 2016[89] compared the practical management of leakage through. 3 techniques were presented: peri-prosthetic silicon collar placement, injection of hyaluronic acid into the tracheoesophageal wall and the combination of the 2 techniques. In addition, a method to reduce the diameter of the tracheoesophageal fistula by removing the voice prosthesis and placing a nasogastric tube through the fistula was also shown. Peri-prosthetic leakage occurred in 6 of the 41 included patients. They were treated with silicone collar, hyaluronic acid injection or combination of both techniques. An increased device life of 56 days (range 7-118 days), 32 days (range 3-55 days) and 63 days (range 28-136 days), respectively for the different techniques was found.

Fukuhara et al 2016[90] studied the quality of life effects of Provox®2 prosthesis in a 17-year old patient that had undergone total laryngectomy. The patient was studied until the age of 21. The study demonstrated that this patient improved the scores for the questionnaires over time and that the advantages of this technique may increase once the patients reach working age.

Erdim et al 2016[91] presented an application of silicon ring expanding the Provox® and Provox®2 voice prostheses in patients with large and persistent peri-prosthetic fistula that experienced difficult leakage problems. They concluded that this was a successful treatment and that device lifetime and speech quality was not affected by these modifications.

4.2 Aerodynamic Characteristics – Phonatory Effort

The in-vivo aerodynamic characteristics total flow, volume range, and intra-tracheal pressure of new and dysfunctional (removed for leakage due to biofilm formation) Provox®2 voice prosthesis were not significantly different; the only parameter that was significantly different was the airflow resistance which was significantly reduced in the dysfunctional prostheses. Unlike in other prostheses where the resistance is known to increase, the resistance in dysfunctional Provox®2 prostheses decreases, which confirms the observation that most Provox®2 prostheses are replaced for leakage problems and not for increased speaking resistance[92].

Kress et al.[93] measured and compared in-vitro airflow characteristics of a variety of voice prostheses used in Europe. Their results showed that the resistance for the patient caused by the prosthesis is mainly determined by the diameter of the device. The airflow resistance of the Provox® and Provox®2 voice prostheses in the speaking range was lower than the airflow resistance of the Blom-Singer Indwelling 16 Fr and 20 Fr, the Blom-Singer Advantage 20 Fr, and the Adeva Highflow prostheses. The airflow characteristics of increased resistance prostheses, intended to provide increased resistance at low airflows created during swallowing and inhalation, showed that the different strengths of Provox® ActiValve® prostheses indeed provided higher opening pressures followed a subsequent steep decrease resulting in low airflow resistance in the speaking range. The other increase resistance prostheses that were tested (Eska Herrman flexion 60, flexion 75, and flexion 90, and Blom-Singer increases resistance 20 Fr) all showed increased resistance in the low airflow range but also in the speaking range, resulting in higher resistance during speaking.

4.3 Success after Extensive Reconstruction

Benazzo et al.[94] describe good voice results with the Provox®2 for voice restoration after circumferential pharyngolaryngectomy with free jejunum repair in 6 patients.

4.4 Microbiological Studies

In an observational study Ticac et al.[95] determined the presence of individual microorganisms and the most frequent microbial combinations in the biofilm of the Provox®2 voice prosthesis in situ and the influence this has on mean and median device life. 85 patients in 5 years received a Provox®2. 100 voice prostheses were microbiologically processed immediately after replacement. Out of 292 isolates, 67% were bacteria and the remaining 33% were yeast. In 83% both bacteria and fungi were present on the prosthesis. Mean device life was 238 days (median 180 days), but life times differed significantly according to the composition of biofilm.

Nowak and Kurnatowski[96] described a study investigating Candida biofilm formation on silicone voice prosthesis, using C. Albicans and C. Krusei fungal strains with Provox®2 and Provox® ActiValve voice prosthesis. Scanning electron microscopy revealed that Candida biofilms formed on voice prosthesis had highly heterogeneous structure and were composed of blastospores, pseudohyphae, hyphae and germ tubes encased in an extracellular material. Noticeable differences in biofilms structure depended on Candida species and type of voice prosthesis.

Holmes et al.[97] studied whether a bovine milk product containing anti-Candida albicans immunoglobulin A antibodies ("immune milk") could reduce the adherence of C albicans to voice prosthesis silicone in vitro, and whether administration of the milk could reduce C albicans colonization and voice prosthesis damage in vivo. An in vitro assay of C albicans attachment to silicone was developed with radiolabeled C albicans. A pilot crossover in vivo trial, over 3 periods of 3 months, was also undertaken for 4 patients with voice prostheses (Provox®2), comparing daily administrations of immune milk and a control milk product. The prosthesis valves were replaced at each changeover and were assessed for wet weight of removable biofilm, yeast numbers in removable biofilm, valve leakage, and valve damage. Authors found that immune milk inhibited C albicans adherence to silicone in vitro. However, in a small clinical pilot study, this effect was not replicated. The conclusion of this study was that there is scope to further investigate the topical use of immune milk for management of voice prosthesis biofilms.

4.6 Accessories

In addition to the Provox® Brush, the Provox®2 voice prosthesis can also be cleaned with a Provox® Flush that flushes water or air through the prosthesis. An in-vitro study has shown that the use of the Provox® Flush has a cleansing effect on the Provox®2 voice prosthesis[98].

5 The Provox® Vega™ voice prosthesis with Provox® SmartInserter™

In 2009, the third generation voice prosthesis Provox® Vega™ was introduced with the new SmartInserter insertion technique. The features and characteristics of this new prosthesis are similar to the Provox®2. The housing and valve are molded in silicone rubber and the valve seat is made of fluoroplastic. The walls of the voice prosthesis are thinner enabling a larger inner to outer diameter ratio. In 2014 the Provox® Vega™ XtraSeal™ with an additional enlarged esophageal flange was introduced with the intention to solve problems with leakage around the prosthesis.

5.1 Device Life, Success Rates, and Complications

The first results of this prosthesis were published by Hilgers et al.[99] in a prospective, short term (2/3 weeks), Phase I feasibility study. No complications were noted during observation time and the prosthesis was noted to have good feasibility. Speech was noted to be better and speaking effort lower with larger diameter prostheses. Subsequently, Hilgers et al.[100] completed a phase II study in two cohorts (one for Provox® Vega™ 20 Fr and one for Provox® Vega™ 22.5 Fr). Each included data for 25 prosthesis changes. The mean was not available for the Provox® Vega™ 22.5 since some devices were still in situ. Results indicated that the device life of Provox® Vega™ is comparable to Provox®2. The median device life for Provox® Vega™ 22.5 was 74 days and the median device life was 93 days for Provox® Vega™ 20 (mean 111 days).

Hancock et al.[101] and Ward et al.[102] conducted a prospective randomized cross-over trial in 31 patients. Hancock et al.[101] reported on patient preference and clinical aspects. Results showed that the majority of patients preferred Provox® Vega™ over the comparator device (Blom-Singer Classic Indwelling). Patients reported better overall voice and speech with the Provox® Vega™ (72 % Provox® Vega™, 14 % Blom-Singer) particularly for better clarity of speech, fluency, volume and less speaking effort. In addition patients reported a preference for Provox® Vega™ for cleaning and maintenance. Ward et al.[95] reported on the perception of voice quality from both clinicians and patient. Results showed that both patients and clinicians perceived voice

to be better with Provox® Vega™ over the comparator device (Blom-Singer Classic Indwelling). Perceptual judgments by clinicians rated the Provox® Vega™ speech to be less strained, easier to understand, less effortful and the better speech overall.

Lorenz & Maier[103] conducted a prospective study in which 19 Provox® voice prosthesis users were fitted with a Provox® Vega™. Patients completed structured questionnaires on subjective evaluation of voice quality, phonation times and dynamic ranges. Patients were asked their opinion about the replacement procedure. Clinicians were asked to evaluate the ease of use of the new insertion device. Patients reported Provox® Vega™ to be superior compared to their previous Provox®2 in terms of voice quality, loudness and pitch modulation. Mean maximum phonation time improved from 11.3 (SD±9.3) to 15.3 (SD±9.7) and dynamic loudness range increased by 4.7dB. Device life of the new Provox® Vega™ prosthesis was 87.8 days (SD±45.8; median 88), which was lower than the device life times of the two previous Provox®2 voice prostheses (141.1 days (SD±91.2; median 140, and 135.9 days (SD±70.1; median 110) respectively. However, the authors indicate that these figures might be biased by the patient selection (i.e. patients that came in for a replacement during the study period might overrepresented patients with short device lives) and duration of the study (i.e. the 9 month study period was too short for observation of longer device life times). Overall, the Provox® SmartInserter™ was considered easy to use and quick. Patients were not uncomfortable during procedure, and when insertion was achieved at the first attempt, patients preferred the new system over the old system because it was quicker. The authors conclude that with a proper training the new insertion system is an improvement over the old Provox®2 method.

In a poster presentation, Schäfer et al.[104] compared the device life of Provox® Vega™ to Provox®2 in 40 patients and found no statistical differences between device life time of these two types voice prostheses in these patients. Authors concluded that the Provox® Vega™ is a safe and reliable voice prosthesis and for these parameters equivalent to the Provox®2.

Hancock et al.[101] performed a prospective randomized cross-over trial in 31 patients comparing two indwelling voice prostheses; the Provox® Vega™ and the Blom-Singer Classic Indwelling. The study focused on patient perceptions and preferences concerning the two devices. The majority of patients preferred Provox® Vega™ over the comparator device. Cleaning and maintenance, voice quality and speaking effort were main reasons for patient preference.

In a follow-up study, Hancock et al. monitored 23 patients for device life and reasons for replacement of the Provox® Vega™. Initial device life data revealed 67 % had functioning devices at 3 months, 52 % at 6 months and 29 % at 12 months. Average device life was 207 days (median of 222)[105].

In a prospective, non-randomized study, Kress et al. 2014[106] compared device life of more recent indwelling voice prostheses Provox® Vega™ and Blom-Singer Dual Valve to device life of well-known standard devices (Provox® 2, Blom-Singer Classic). Average overall life time was 108 days, median 74 days. The prosthesis with the longest dwell time was the Provox® ActiValve® (median 291 days). Provox® Vega™ had longer device life compared with Provox®2 (median 92 days vs 66 days; p = 0.006) and compared with Blom-Singer Classic (median 92 days vs 69 days; p = 0.004). There was no significant difference between the device life of Blom-Singer Classic versus Provox®2 (p = 0.604), Blom Singer Dual Valve versus Provox®2 (p = 0.233) and versus Provox® Vega™. The authors concluded that device lifetimes of Provox® Vega™ and Provox® ActiValve® were better than those of Provox®2 and the Blom-Singer Classic. New voice prostheses, with a defined valve opening pressure (Provox® Vega™, Provox® ActiValve®, Blom-Singer Dual

Valve) had longer lifetimes than prostheses without a defined opening pressure (Blom-Singer Classic and Provox®2).

In a multicenter prospective crossover study by Serra et al. (2017)[107], Provox 2 and Provox Vega were evaluated in terms of device life and voice outcome. Enrolled patients were categorized and divided into four groups based on age, postoperative radiation therapy and gastroesophageal reflux disease. In three out of four patient groups ("normal", "radio-treated" and "elderly"), average recorded prosthetic lifetime was significant improved for Provox Vega over Provox 2. Overall, average lifetime was 146 days for Provox2 and 182 days for Provox Vega (P=0.046). The perceptual voice data showed a better rating across all parameters for the Provox Vega samples. The authors concluded Provox Vega having a longer device life and better perceptual voice parameters compared to Provox 2.

Robinson et al. 2017[108] conducted a prospective study, comparing intraoperative voice prosthesis placement with delayed voice prosthesis insertion. The device life of the initial intraoperative placed voice prosthesis was 159.7 days, compared to 24.5 days for delayed insertion. Intraoperative placement with Provox Vega was further associated with earlier voicing (13.2 vs 17.6 days), less changes due to resizing (8% vs 80%), reduced hospital stays (17.2 vs 24.5 days) and cost savings. The authors conclude superior clinical and patient benefits to be associated with intraoperative voice prosthesis placement with Provox Vega.

Mayo-Yáñez et al.[109] found non-significant differences in terms of device life between Provox Vega and Provox 2 in their case-crossover study published in 2018. The study involved data from 34 laryngectomized patients that was retrospectively analyzed. The patient selection criteria was having a minimum of three replacements with each type of prosthesis. Both prostheses had a median device lifetime of 74 days. The authors concluded that randomized prospective studies with adequate sample sizes are needed to offer more robust and reliable results.

In a retrospective cohort study by Petersen et al. 2019[110], long-term results of device life of Provox VPs were published. Data from medical records over a period of 13 years (Jan 2000 – Dec 2012) was collected for a total of 232 patients. The overall median device lifetime of the standard VPs used in the study period (i.e. the regular Provox2 (n=1664), and Vega (n=1136) prostheses) were not significant different: Provox2 (median 63 days, 95% CI 61-68), and Vega (median 66 days, 95% CI 63-71).

Provox Vega XtraSeal was evaluated in terms of efficacy, device life satisfaction and ease of placement in a study by Petersen et al. 2018[111]. All included patients (n=13) had a history of periprosthetic leakage and early device failure. Median device lifetime of the former VP before placement of the first Provox Vega XtraSeal was 38 days (95% CI 1–76). With Provox Vega XtraSeal, the median device life was 68 days (95% CI 56-80), which is comparable to median device lifetimes of the Provox2 (63days) or Provox Vega (66 days) reported in literature[110]. Almost all cases of periprosthetic leakage could be solved with the Provox Vega Xtra-Seal. Only in one patient the device had to be replaced due to periprosthetic leakage. The authors concluded that Provox Vega XtraSeal is a valuable tool for solving periprosthetic leakage.

6 The Provox® Vega™ Puncture Set

The Provox® Vega™ Puncture Set (PVPS), based on the Seldinger technique, is a disposable, sterile set of instruments for primary and secondary tracheoesophageal puncture (TEP) and immediate voice prosthesis insertion. The set consists of a curved Puncture Needle to create the TEP, and a GuideWire and a Dilator with a pre-mounted Provox® Vega™ voice prosthesis for the dilation of the TEP and the actual introduction of the Provox® Vega™ voice prosthesis. The set also contains a Pharynx Protector, only to be used for primary TEP during TLE. For secondary punctures traditional methods of pharynx protections, such as a rigid esophagoscope should be used.

After establishing adequate pharynx protection, the Puncture Needle is used to create the TE puncture, then the GuideWire is fed through the puncture needle, the Puncture Needle and Pharynx Protector are removed, leaving the GuideWire in situ. Then the Dilator is attached the GuideWire, and use for dilatation of the TE puncture followed by placement of the Provox® Vega™ voice prosthesis.

The PVPS is available with 17Fr, 20 Fr, and 22.5 Fr Provox® Vega™ voice prostheses, in the lengths 8 mm, 10 mm, and 12.5 mm. The 17 Fr version is also available in 15 mm.

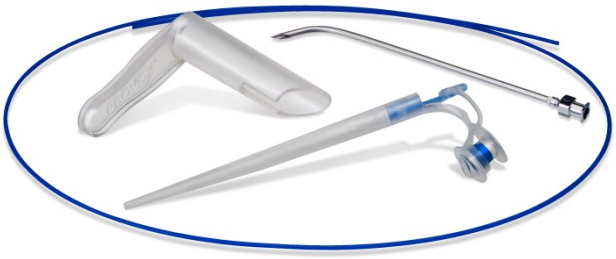

Figure 8 The Provox® Vega™ Puncture Set (PVPS).

Hilgers et al.[8] describe the results of a multicenter prospective clinical feasibility study investigating the PVPS that was performed in 4 countries and 5 institutions. The publication describes the various investigations conducted during the development of the PVPS, including the results obtained with the final design of the device in 27 patients (20 primary punctures and 7 secondary punctures). All procedures were successful, in 89% (24/27) of the procedures no additional instruments were needed to place the voice prosthesis, in the remaining 3 procedures hemostats were needed to full the tracheal flange of the voice prosthesis in place. Participating surgeons rated appreciation, ease of use, time consumption and estimated surgical risks using the PVPS as better compared to the use of the traditional Provox surgical tools used.

The PVPS was also evaluated by Lorenz et al. in 21 patients[112]. The average surgical time was 83.5 sec for primary voice prosthesis insertion and 212.57 sec in secondary procedures. The prosthesis could be inserted without complication in 19 patients, while a longer prosthesis needed to be selected intra-operatively in two patients due to a thick membranous wall. No serious complications were observed. Authors conclude that the PVPS proved itself to be a safe aid in the insertion of voice prostheses, that is significantly easier to use than other systems and tissue trauma is minimal.

In a retrospective chart review by Fukushima et al. 2017[113] secondary indwelling voice prosthesis insertion (Provox2 and Provox Vega) after total pharyngolaryngectomy (TPL)with free jejunal reconstruction were analyzed. Satisfying communication outcome with Provox insertion was reported for 78.4% of patients (102/130). Communication outcomes were similar regardless of the insertion site (46 patients with jejunal insertion, 84

with esophageal insertion). Complications rate for Provox devices were significantly lower than seen in previous studies. When the Provox Vega Puncture Set was used, the complication rate was as low as zero.

Ricci et al. 2018[114] used the Provox Vega Puncture Set for retrograde placement of voice prosthesis during secondary TEP in 15 patients. All prostheses were successfully and immediately placed. Good voice restoration and understandable voice was maintained for all patients after 2 months. The authors concluded that secondary TEP is safe and effective with Provox Vega Puncture Set.

7 The Provox® ActiValve®

In 2003, a new problem-solving Provox® voice prosthesis was introduced to the market. This voice prosthesis is especially developed for laryngectomized patients with very short device life times (less than 4 to 8 weeks) of their current prosthesis. Those extremely short device life times may be caused by excessive Candida growth or by underpressure during swallowing and/or inhalation forcing the valve open. This underpressure causes extremely early or sometimes immediate leakage and can be diagnosed by observing the valve of the prosthesis while the patients swallow and inhales.

The first results of this prosthesis, the Provox® ActiValve®, were described by Hilgers et al[6]. Eighteen patients with an average device life of 30 days were included in the study. Device life increased on average 14 times (range 3-39). At the time of analyses 7 prostheses were removed for leakage after an average of 278 days (increased from average 21 days with previous prosthesis), and 7 prosthesis were still in situ for and average for 344 days (increased from 36 days with previous prosthesis). These findings have been confirmed in a long-term study[115] in a cohort of 42 laryngectomized patients with a median device life of their Provox®2 voice prosthesis of 21 days. The median device-related device life time of the Provox® ActiValve® prostheses replaced for leakage through the device or still in situ at the point of data collection was 337 days: a 16 fold average increase in device life time ($p<.001$). Fistula related reasons (10 patients, after a median of 68 days) for replacement included esophageal pouch (N=4), granulation (N=3), extrusion (N=2), and peri-prosthetic leakage (N=1).

In a prospective study, Graville et al.[116] investigated whether the Provox® ActiValve® results in increased device-life in 11 individuals with below average device-life. This study also looked at cost-effectiveness and impact on voice-related quality of life. The majority (73%) experienced significant improvement as a result of use of the device. Those who continued to wear the device were followed for an average of 30.45 months (range, 14.70–43.49 months) and wore a total of 31 devices over this time. They demonstrated an average increase in device-life of more than 500%, going from an average of 1.93 months with a traditional indwelling device to 10.30 months with the Provox® ActiValve®. Voice-related quality of life was not significantly different from that of a group of controls. Overall satisfaction with the device was high. Overall, there were estimated to be cost savings to third-party payers through use of the Provox® ActiValve® in this population.

In a retrospective cohort study by Petersen et al. 2019[110], long-term results of device life for several generations of Provox VPs were published. Data from medical records over a period of 13 years (Jan 2000 – Dec 2012) was collected for a total of 232 patients. ActiValve VPs had significantly longer median device lifetimes than that of the regular VPs: ActiValve Light 143 days (95% CI 111-211), and ActiValve Strong 186 days (95% CI 132-245), compared to Provox2 63 days (95% CI 61-68) and Vega 66 days (95% CI 63-71).

7.1 Microbiological Studies

Timmermans AJ et al. 2015[117] investigated the composition and diversity of biofilm of both the silicone and the fluoroplastic material of the Provox® ActiValve® and whether it is susceptible to destruction by Candida. Thirty-three voice prostheses (Provox® ActiValve®) were analysed with Illumina paired-end sequencing (IPES), interaction with fluorescence in situ hybridization (FISH), and confocal laser scanning microscopy (CLSM). Results showed that Candida albicans and Candida tropicalis are dominant populations on fluoroplastic and silicone, yet microbial diversity is significantly lower on fluoroplastic. They concluded that the fluoroplastic material of Provox® ActiValve® seems insusceptible to destruction by Candida species, thus extending life time of the voice prosthesis.

Leonhard et al. 2017[118] compared biofilm resistance of different valve flaps on modern voice prostheses in an in vitro biofilm model. Five different voice prostheses were incubated for 22 days with a multispecies bacterial-fungal biofilm composition. In comparison to the other prostheses investigated in the study, Provox® ActiValve® showed significantly less surface biofilm formation. The authors concluded that the use of Teflon as valve flap material gives Provox® ActiValve® a stronger resistance to biofilm formation in vitro.

8. The Provox® NID™ voice prosthesis

In 2005, the non-indwelling Provox® NID™ voice prosthesis was introduced. This prosthesis is intended for safe and easy replacement by the patient him- or herself and is available in 2 different outer diameters: 17 French and 20 French. The first results were published by Hancock et al.[7]. Fifteen non-indwelling Blom-Singer Low Pressure users converted to the Provox® NID™. In vitro tests showing the more favorable characteristics of the Provox® NID™ were confirmed by the patients reporting less effortful and clearer speech. The pull-out force of the Provox® NID™ was significantly higher than that of the Blom-Singer valves. Accidental aspiration of the Provox® NID™ did not occur, while 21% of the patients had experience aspiration of their previous prosthesis.

In 2014, Lewin et al.[119] completed a longitudinal eight year retrospective cohort study on 186 patients who used the NID. Results suggest that the Provox® NiD™ offers high patient satisfaction, better than expected durability in patients with early leakage, and favorable voice quality. The median device life of all Provox NiD™ VPs was 30 days; 45 days for removal due to prosthetic leak, 15 days for removal due to other indications. The median device life of the Provox® NiD™ (based on removal due to prosthetic leak) was significantly longer than that of other non-indwelling VPs (45 vs 29 days, p=0.0061) and did not differ significantly from that of standard indwelling VPs (45 days vs 50 days, p=0.4263).

8.1 Conversion from non-indwelling to indwelling

In some countries, the use of non-indwelling voice prostheses is more common than others. In South-Africa, historically, the non-indwelling types of prostheses are used more often. A study by Vlantis et al.[120] showed that replacing the non-indwelling prosthesis (Blom-Singer Low Pressure, Duckbill or Bivona type) with a Provox®2 voice prosthesis was technically simple, and led to an improvement in voice quality and patient satisfaction. The majority of patients (92.3%) preferred the Provox®2 voice prosthesis compared to the non-indwelling prosthesis.

9 Factors influencing device life time

Ol'shansky et al.[121] (article in Russian) investigated biofilm formation on Provox® (N=16) and Blom-Singer (N=11) voice prosthesis after usage of 6 months to 2 years. Prophylactic use of antifungal drugs prolonged device life two-fold. An in vitro study on the influence of dairy products on biofilm formation on voice prosthesis showed that the formation of biofilm on prostheses can be lessened by the daily use of certain dairy products, buttermilk having the greatest effect[122]. Application of a buccal adhesive Nystatin tablet was found to be more effective than placebo[123] and more effective than local cleaning of the prosthesis with Nystatin suspension on the Brush[124].

An in in-vitro and in vivo study investigated the influence of daily consumption of Buttermilk and Yakult Light fermented milk on device life time of Provox®2 voice prostheses in 18 patients (10 Yakult Light group, 8 Buttermilk group) and the influence of the same product in vitro[125]. The number of prostheses during the 6 months trial duration were compared with the number needed in the prior 6 months. Patients with a mean device life time of less than 75 days during the past 6 months were included. In the Yakult Light group (mean in situ life time 33 days), device lifetime increased 3.76 times, during the 6 month trial 39 prostheses were used and during the previous 6 months 64 prostheses were used. In the Buttermilk group (mean in situ life time 34 days), device lifetime increased 1.28 times, during the 6 month trial 51 prostheses were used and during the previous 6 months 59 prostheses were used. In-vitro test results showed that Yakult Light reduced the amount of bacteria with 22%, but that yeast colonization was stimulated up to 21%; Buttermilk reduced the amount of bacteria to 60% and stimulated yeast colonization up to 483%. The authors concluded that Yakult Light fermented milk drink reduced biofilm formation on Provox®2 voice prostheses and significantly increased device life time. Van Weissenbruch et al.[123] investigated the influence of a buccal bioadhesive slow-release tablet containing miconazole on Provox® device lifetime in 36 laryngectomized patients and found that the device lifetime was significantly higher in patients treated with the use of the table containing antimyotic agents compared to the placebo group (9.3 versus 5.6 months). Ozkul et al.[73] report a low incidence of fungal colonization which they believe is due to daily consumption of Turkish yoghurt and Kephir.

Holmes et al.[97] published in 2012 whether a bovine milk product containing anti-Candida albicans immunoglobulin A antibodies ("immune milk") could reduce the adherence of C albicans to voice prosthesis silicone in vitro, and whether administration of the milk could reduce C albicans colonization and voice prosthesis damage in vivo. Authors found that immune milk inhibited C albicans adherence to silicone in vitro. However, in a small clinical pilot study, this effect was not replicated. The conclusion of this study was that there is scope to further investigate the topical use of immune milk for management of voice prosthesis biofilms.

Buijssen et al.[126] investigated 26 Provox®2 voice prostheses and 8 Groningen Ultra Low Resistance voice prostheses that were removed for leakage through or increased resistance. Thirty-three of the 34 explanted voice prosthetic biofilms contained lactobacilli in close association with the Candida species present. Boscolo-Rizzo et al.[77] found that device life time of the prosthesis is significantly influenced by radiotherapy and GERD. The mean in situ device life was 163.3 days in irradiated and 202.9 days in radiated patients. The mean in situ device life was 126.5 days in patients with and 215.7 days in patients without endoscopic evidence of erosive ulcerative gastroesophageal reflux disease (GERD). These findings regarding the influence of GERD was supported by Lorenz et al.[127], who found in a 2-year prospective non-randomized study a relationship between pathological supraesophageal reflux and the occurrence

of tracheoesophageal puncture complications, especially severe puncture enlargement, in patients who underwent total laryngectomy and prosthetic voice restoration. A significant correlation was found between the occurrence of tracheoesophageal puncture complications and the severity of supraesophageal reflux. It was concluded that an enlarged puncture is not device related, but related to the presence and severity of reflux[128].

Fusconi et al. 2014[129] tested 9 Provox®2 voice prostheses through photographic and electron microscopic assessment and found that the silicone undergoes a degenerative process, thus causing the surface to become rough, deformed, swollen, and translucent. The authors concluded that the degenerative process of the silicone seems to be related to the oxygen present in the trachea and esophagus and to the production of oxygen-free radicals on the biofilm's part and the immune system.

Somogyi-Ganss et al 2016[130] studied the correlation of oral health and microbial colonization with lifetime of voice prostheses (not specified). Two subgroups were analyzed: (1) patients with microbial analysis of the VP and the mouth were analyzed to identify patterns of common contamination, and (2) patients who were prescribed targeted oral decontamination on the basis of the microbial analysis of the VP were analyzed to evaluate effects on device life. In the TEP-oral microflora subgroup (n = 15), 7 had common microorganisms in the mouth and on the VP. After targeted decontamination, the median device life of prostheses improved from 7.89 to 10.82 weeks (p = 0.260). The majority of patients with a suboptimal VP device life in this pilot had polyspecies bacterial and fungal colonization. The authors conclude that an increase in voice prosthesis lifetime can be reached by using targeted decontamination treatment to patients.

In a retrospective cohort study by Petersen et al. 2019[110], long-term results of device life for several generations of Provox VPs were published. compared with a previous cohort study published by Op de Coul et al. 2000[131] at the same institute. Petersen et al. found that the observed median device lifetime for regular VPs (Provox 2 and Provox Vega) was noticeably lower compared to the historical cohort. Potential explanations for the shorter device lifetime according to the authors are the increasing numbers of TLs after prior (chemo)radiation since 1990. In the 2019 cohort 68% of patients had (chemo)radiotherapy as their primary treatment compared to 45% in the historical cohort. Another potential explanation mentioned for the shorter device life is the improved method of replacement of VPs used today. In the 2000 cohort the uncomfortable method of retrograde placement was still used. With the introduction of anterograde placement, the threshold for patients to ask for replacement in case of minor leakage might have decreased. Furthermore, a surprising finding for the authors were the highly significant relation between longer device lifetimes and driving distance to the hospital. A third explanation would therefore be that closer distance to nearest hospital makes a visit for replacement less of a burden. This hypothesis is supported by the longer device lifetimes reported from countries such as Australia, where driving distances are significantly longer than in the Netherlands. Hancock et al 2012[105] reported the median device life time of Provox Vega to be 222 days in an Australian cohort.

A mean device life of 16 months for Provox Vega was reported in a study by Krishnamurthy et al 2018132. The study included 60 laryngectomized patients rehabilitated with voice prosthesis at a cancer center in South India. The findings were questioned in a "Letter to the Editor" by Mayo-Yáñez 2019133 due to the much higher device-life time than the one shown in literature in general. Mayo-Yáñez questioned the fact that the motive of vp-replacements, as well as the potential psychosocial and financial burden for the patient, had been left out from the discussion. When comparing

device lifetimes between studies, patient characteristics and voice prosthesis reimbursement should be taken into account.

10 Complications

This section summarizes some publications that describe specific complications, treatment methods of specific complications, or a case of an unusual complication.

Brasnu et al.[134] describe their treatment of enlarged TE fistula's, the prostheses used in their patients were Blom-Singer, Groningen High-Resistance, Traissac, and Provox® (no information is given as to the numbers of each prostheses used and their relationship with enlarged fistula). Leakage around the prosthesis was seen in 45.5% of the patients (31 out of 68 patients). In 11.8% (8 patients) it was inconsistent and non-symptomatic and it resolved without treatment. Twenty-three patients received treatment for an enlarged fistula; since more treatments than patients are reported we have to assume that some patients received several treatments. Twelve events were treated simply by changing the voice prosthesis, 17 events by temporarily inserting a smaller catheter, 9 events with collagen injection, and one with electro coagulation.

Luff et al.[135] reported a case of intractable leakage around that could not be solved with a different valve size, the case was solved by injection of Hyloform®, a colorless viscoelastic gel, circumferentially around the puncture. Other solutions for intractable leakage around the prosthesis published in the literature are treatment with local GM-CSF104 or Bioplastique®[136, 137] and surgery[138].

A very rare complication was described by Hiltmann et al.[139]; the remainder of a Provox® prosthesis that was pushed through into the esophagus (after cutting of the tracheal flange during a normal replacement procedure) got stuck in Bauhin's valve and cause a mechanical ileus.

Scheuermann and Delank[140] describe a case of perforation of the posterior esophageal wall with an abscess of the mediastinum in a patient who first underwent transoral laser surgery, then total laryngectomy with primary puncture and placement of a Provox® prosthesis followed by chemoradiation. A similar complication was reported by Bozzo et al.[141] who described this problem as a consequence of inadequate pharynx protection during secondary TE puncture.

Counter et al.[142] describe a case of esophageal obstruction caused by the impaction of the portion of the Provox®2prosthesis (that was removed by cutting the tracheal flange of and pushing the remainder of the prosthesis into the esophagus, which is not recommended) on a previously undiscovered benign esophageal stricture.

Smith et al.[143] describe the use of KTP laser for managing hypertrophy and granulation around the voice prosthesis. Gonzalez-Garcia et al.[144] describe the growth of granulomatous tissue in three patients to such an extent that an esophagoscopy was needed to extract the prosthesis.

Hadzibegovic et al.[145] investigated the relationship between pepsin concentration in saliva and the occurrence of tracheoesophageal fistula (TEF) complications and voice prosthesis (VP) complications. The concentrations of pepsin in the saliva of 41 laryngectomized patients were correlated with the incidence of TEF complications (periprostethic leakage, atrophy, esophageal mucosa hypertrophy, granulations, fistula enlargement, and VP dislocation), VP complications (transprosthetic leakage, Candida infection) and voice quality. In all, 17 (42%) patients had complications. Median value of

pepsin concentration in all patients was 4.8 (range 81.7). Median pepsin concentration was not statistically significant higher in patients free of TEF or VP complications (6.6 vs. 3.2; p=.118). In addition, statistically insignificant negative correlation between pepsin levels and voice quality measured by HRS scale (Spearman's rho, p > 0.05). Authors conclude that, although reflux was proposed as cause of TEF complications and pepsin has been proven as a most sensitive and specific marker of extra-esophageal reflux, they did not find any statistically significant correlation between pepsin levels and occurrence of TEF or VP complications.

Lorenz et al.[146] assessed epithelial-mesenchymal transition in 148 consecutive biopsies from 44 patients with/without fistula enlargement under dual-probe pH monitoring before and after proton-pump inhibitor (PPI) therapy. Results showed that epithelial-mesenchymal transition correlates with severity of reflux and presence of fistula enlargement in patients who underwent prosthetic voice rehabilitation, but epithelial-mesenchymal transition seems to be reversible upon PPI treatment in early stages only.

A more recent study by Lorenz et al. 2016[147] described two rare cases of fistula-related complications which showed a rapid development of granulation tissue around the voice fistula, leading to complete incarceration of the Provox® voice prosthesis and subtotal/total stenosis of the neopharynx.

Calkovsky et al 2015[148] reported a case of a 48-year-old man with secondary Provox® voice prosthesis insertion 16 months post laryngectomy. On the 6th day after the insertion, TEP decayed. After prosthesis removal the tissue defect was sutured. The study suggests that while the overall risk of severe complications seems relatively low, some complications might be challenging and might require specific management.

11 Peer-reviewed overview articles and editorials

In 2011 Balm et al. published an overview article on the use of indwelling voice prostheses[130]. The article states that, since indwelling devices may have a more robust construction, their device-life generally is longer than that of their non-indwelling counterparts. Indwelling devices are described also to have the unique advantage in that patient's dexterity plays a lesser role in the daily maintenance of the device. With a few refinements in the surgery of TLE several postlaryngectomy problems can be avoided or diminished such as hypertonicity of the pharyngoesophageal (PE) segment and a poor contour of the stoma. The combination of Heat and Moisture Exchanger (HME) and indwelling voice prosthesis contributes to a significant improvement of both pulmonary function and voice quality. The solution of the majority of prosthesis and TE-fistula related problems by the well trained physician, make prosthetic voice restoration a safe procedure[149].

Lorenz KJ. 2015[150] conducted a literature review on the development and treatment of periprosthetic leakage after prosthetic voice restoration and compared the results with a retrospective analysis on the treatment of 232 patients from 1994 to 2013. 22.5-French voice prostheses (Provox®, Provox®2, Provox® Vega™, Provox® Activalve®) were used. During the study period, the incidence of periprosthetic leakage was 35.7 %. Substantial enlargement of the tracheo-oesophageal fistula which required multiple treatments occurred in 12.5 % of the patients. Granulation tissue that required treatment developed in 43 patients. Lorenz concluded that most problems with voice prostheses are minor and can be easily managed. Tracheo-oesophageal fistula enlargement and periprosthetic leakage is, however, a serious problem. Voice prosthesis diameter and postoperative radiotherapy alone can be largely ruled out as underlying causes. By contrast, reflux disease and radiochemotherapy can considerably elevate the risk of fistula leakage.

12 Summary

In summary, the large amount of literature shows that all types of Provox® voice prostheses are used successfully worldwide. Device life may differ and is most likely influenced by dietary habits and economic factors. The values reported may also differ due to the definition used to determine device life. Most studies report prosthesis related device life only, but some also include puncture-related changes such as downsizing. Table 1 summarizes the data for device life found in the various studies. Interpretation of the results is sometimes difficult due to the fact that some studies have used averages and some have used medians. The medians are usually lower than the averages since they do not account for the extremely long device lives that some patients have. Complication rates are acceptable and may differ due to definitions used in describing complications, but also due to treatment and prevention. If dealt with in a timely manner, most complications can be resolved easily and before becoming serious.

Table 2 summarizes the data found for complications, while Table 3 represents the success rates with Provox® voice prostheses.

Table 1. Overview of device life time of Provox® prostheses.

Authors	Prosthesis	Device Life	Comments
Hilgers et al., 1990[4]	Provox®	Mean 154 days	Prospective 79 patients, 67 converted from Groningen, 12 primary insertion
Balle and Thomsen, 1993[9]	Provox®	Provox®: 6-8 months Duckbill: 1-3 months	Retrospective may 1989 – august 1992 24 patients, converted from Bivona Duckbill
Van Weissenbruch & Albers, 1993[10]	Provox®	Average 5.4 months	Prospective Feb 1991 – Feb 1993 37 patients 72 changes
Hilgers et al.1993[11]	Provox®	Mean 235 days Median 141 days Longer in laryngeal cancer (7.4 months) compared to hypopharyngeal cancer (4.3 months); longer in unirradiated (9.6 months), than in pre-op radiation (6.1 months) or post-op radiation (5.8 months)	Prospective 132 patients

Authors	Prosthesis	Device Life	Comments
Heaton and Parker, 1994[12]	Provox® (16) Groningen HR (83) Groningen LR (71)	Provox® mean 4.1 months, median 2 months GHR mean 6.0 months, median 4 months; GLR mean 4.4 months, median 3 months. Differences not statistically significant	Prospective consecutive structured data collection oct 1986 – august 1993 49 patients 203 prostheses Groningen prostheses were relatively more often changed for increased speaking resistance than Provox® prostheses
Callanan et al, 1995[13]	Provox®	Mean 148 days Median 120 days	Cohort study 28 patients
Van den Hoogen et al., 1996[14]	172 Provox® 220 Nijdam 453 Groningen (higher number of Groningen because this was the only one available up to 1990)	Provox® mean 13 weeks Groningen mean 15.8 weeks Nijdam 19 weeks	Prospective, randomized replacement of current vp (Groningen) for one of three types jan 1991-july 1993 158 patients 845 consecutive placements Groningen prosthesis relatively more often replaced for increased speaking resistance. Nijdam more often replaced for different type prosthesis due to prosthesis related problems.
Toma et al., 1996[15]	Provox®	Average 148 days	Cohort 31 patients
Ollas et al., 1996[16]	Provox® (95) Blom-Singer indwelling (4) Groningen (2)	Combined for all three types median 327 days	Retrospective June 1991-Nov 1995 101 patients
De Carpentier et al.,1996[19]	Provox®	Median 4.5 months (failure determined as leak around or through (resizing), and inability to produce voice)	Retrospective 39 patients 81 prostheses A small group of patients (7.7%) required frequent replacement and accounted for 24.7% of the valve failures.
Hilgers et al., 1997[5]	Provox®2	Good feasibility Main reason for replacement leakage through	First study on Provox®2 + anterograde replacement

Authors	Prosthesis	Device Life	Comments
Slavicek et al., 1997[17]	Provox® (all secondary puncture)	Median 98 days (range 43-589)	Retrospective 1992-1996 53 patients 372 prostheses
Lacourreye et al., 1997[18]	Provox®	Mean 311 days (33% replaced for leakage through, 27% for leakage around, 24% for deterioration of the prosthesis, and 16% for increased airflow due to crusting.	Retrospective (Nov 1990 –June 1994) 37 patients 100 prostheses
Cavalot et al., 1997[20]	Provox® (16) Blom-Singer indwelling (14)	Mean Provox® 6 months Mean Blom-Singer 5 months	Prospective RCT Provox® vs Blom-Singer 30 patients, 16 Provox®, 14 Blom-Singer
Aust and McCaffrey, 1997[22]	Provox®	Mean 166 days (leakage through in 12.5%, resizing in remainder)	Retrospective 21 patients 24 replacements in 13 patients
Nasser et al., 1997[23]	Provox®	Average 8 months	Prospective Mar 1994 – Sep 1996 52 patients
Delsupehe et al., 1998[24]	Provox® Blom-Singer indwelling	Median Provox® 14.5 weeks Median Blom-Singer 15 weeks	Prospective RCT 52 patients 113 prostheses
Graville et al., 1999[52]	Provox®2 (6) Blom-Singer indwelling (24)	Leakage through the device secondary to yeast colonization occurred with equal frequency in both devices	Retrospective 30 patients
Ackerstaff et al., 1999[53]	Provox®2	Median 104 days	Prospective, multi-center 239 patients
Baumann et al., 2000[25]	Provox® (1992-mid 1997) Provox®2 (mid 1997-1998)	Average 3.9 months in 'successful' rehabilitated and 5.6 months in 'unsuccessful'	Prospective, 1992-1998 105 patients 478 replacements
Biacabe et al., 2000[26]	Provox®	Average 241 days	Retrospective 68 patients 197 replacements
Koscielny and Bräuer, 2000[51]	Provox® Provox®2	Average 6 months	Prospective 45 patients 177 replacements

Authors	Prosthesis	Device Life	Comments
Op de Coul et al., 2000[54]	Provox® Provox®2	Median Provox® 120 days Median Provox®2 92 days Main reason for replacement leakage through (73%). Device life time was significantly longer in patients who had not received radiotherapy and in patients older than 70 years First prosthesis placed at surgery lasted substantially longer than subsequent prostheses	Retrospective Nov 1988 – May 1999 318 patients 2700 replacements
Balle et al., 2000[55]	Provox® Provox®2	Average Provox® 3.1 months Average Provox®2 2.3 months	Retrospective May 1989-May 1999 88 patients Conversion from Blom-Singer (non-indwelling) Duckbill to Provox®
Schafer et al., 2001[58]	Provox® (136) Provox®2 (78) Blom-Singer indwelling (172)	Average Provox® 244 days Average Provox®2 96 days Average B-S 107 days Provox® Significantly longer than Provox®2 and B-S. No significant difference between Provox®2 and Blom-Singer.	Retrospective 1993-1999 58 patients 378 prostheses
Hotz et al., 2002[59]	Provox® Provox®2	In 'early' follow-up phase (0-9 months) device life was longer in 'successful' users (4.2 vs 3.9 months)	Retrospective 1992-1998 82 patients
Fajdiga et al., 2002[60]	Provox® Provox®2 Other (unnamed)	Overall 5.5 months average	Retrospective 32 patients 1998-2002
Elving et al., 2002[72]	Provox®2 (296) Groningen LR (377) Provox® (12)	GLR immediately postop average 180 days GLR 137 days Provox®2 90 days Radiation does >60Gy associated with limited device life time	Retrospective jan 1993-Nov 1999 101 patients 685 prostheses

Authors	Prosthesis	Device Life	Comments
Hilgers et al., 2003[6]	Provox®ActiValve®	Average 14-fold increase in device lifetime compared to device life of Provox®2 in patients with device life problems	18 patients with average device life of 30 days
Cornu et al., 2003[27]	Provox®	Average 303 days (range 10 -1191 days)	Prospective 1995-1998 128 patients 63 replacements
Lequeux et al., 2003[56]	Provox® (24) Provox®2 (128)	Median Provox® 303 days Median Provox®2 144 days	Retrospective March 1993 – Nov 2000 38 patients 152 prostheses
Trussart et al., 2003[61]	Provox®/ Provox®2 (93) Blom-Singer (73) Groningen (5) VoiceMaster (7)	Averages in days: Provox®165.5 Blom-Singer 143.5 Groningen 135 VoiceMaster 195	Retrospective long-term follow up (3 – 16 years)
Makitie et al., 2003[62]	Provox® Provox®2	Average 10 months	Retrospective 1992-2002 95 patients
Ozkul et al., 2003[73]	Provox® (204) Blom-Singer (17) Groningen (5) Turvox (5)	Provox® 18 months Blom-Singer 5 months	231 patients
Demir et al., 2004[63]	Provox®2	Average 24 months	Retrospective 50 patients 60 prosthesis
Hancock et al., 2005[7]	Provox®NID™	Overall average 74 days	Feasibility study in 15 patients, conversion from Blom-Singer Low Pressure
Morshed et al., 2005[64]	Provox®2	Average 216 days	retrospective 21 patients 2 years
Lam et al., 2005[65]	Provox®2 (192) Blom-Singer indwelling (7) Blom-Singer Duckbill (3) Voicemaster (1)	Overall median 8.2 months First prosthesis 9.6 months	Retrospective 1998-2004 60 patients 203 prosthesis
Bien and Okla, 2006[66]	Provox®2	Average 9.8 months in radiated in 9.7 months in non-radiated patients	Retrospective 2002-2004 106 patients 132 replacements

Authors	Prosthesis	Device Life	Comments
Terada et al., 2007[69]	Provox®2	Averages: Laryngeal ca 27.2 weeks Hypopharynx ca 16.6 weeks Overall 21 weeks	Cohort 2002-2004 32 patients
Gonzalez Poggioli et al., 2007[71]	Provox®2 (81) Blom-Singer (7) Herrmann (7) Groningen (1)	Overall average 9 months	Retrospective oct 2000-dec 2005 96 patients
Bilewicz et al., 2007[74]	Provox®2	Mean 295 days	Prospective 39 TE speakers, 10 esophageal speakers
Ramalingam et al., 2007[76]	Provox®2 (21) Blom-Singer Low Pressure (20)	Average Provox®2 15 months Average Blom-Singer 3 months	Prospective comparative
Boscolo-Rizzo et al., 2008[77]	Before Sep 2001 Blom-Singer indwelling After Sep 2001 Provox®2	Average radiated 163.3 days, non-radiated 202.9 days Average non GERD 126.5 days and non-GERD 215.7 days	Retrospective 1998-2006 106 patients 515 replacements
Soolsma et al., 2008[115]	Provox®ActiValve®	Median 337 days (improved from median 21 days with Provox®2)	Retrospective 42 patients with short device life time Long-term follow up
Tammam and Ahmed, 2009[78]	Provox®2	Device life ranged from 5 to 60 months with an average of 24.5 months	Retrospective study 5 patients
Bozec et al., 2010[79]	Provox® and Provox®2	Mean device life for Provox® 7.6 months; Provox®2 3.7 months	Retrospective study 87 patients
Hilgers et al., 2010[100]	Provox® Vega™	Provox® Vega 22.5 median 74 days Provox Vega 20 median 93 days, mean 111 days).	Prospective study, two cohorts 25 prosthesis changes
Schäfer et al, 2011[104]	Provox® Vega™	Mean 70 days; no difference compared to Provox®2	Prospective 40 patients
Graville et al., 2011[116]	Provox® ActiValve®	Mean traditional indwelling device life 1.93 months. With Provox® ActiValve mean 10.30 months	Prospective 11 patients
Boci et al., 2012[84]	Provox® and Provox®2	Mean device life for Provox® ; and Provox®2" 279 days	Prospective, 106 patients

Authors	Prosthesis	Device Life	Comments
Zimmer-Nowicka & Morawiec-Sztandera, 2012[86]	Provox®2	Average 260 days	Retrospective 42 patients
Hancock et al. 2013[105]	Provox® Vega™	Average 207 days; median 222 days	Prospective 23 patients
Lewin et al. 2014[119]	Provox® NiD™, Provox®2, BS Classic, Provox® Vega™, BS non-indwelling Duckbill, BS low pressure, Bivona Ultra low, Bivona Duckbill	Provox® NiD™ (median 45 days)	Longitudinal retrospective cohort study 186 patients
Kress et al. 2014[106]	Blom-Singer Classic, Blom-Singer Dual Valve, Provox®2 , Provox® Vega™ and Provox® ActiValve®	Provox® ActiValve® (median 291 days); Provox® Vega™ (median 92 days; Provox®2 (66 days); Blom Singer classic (median 69 days)	Prospective 102 patients 749 voice prostheses
Chaturvedi P, et al 2014[31]	Provox®	Mean lifespan :18 months, Median 9 months, range 1 to 87 months)	58 patients
Kilic et al. 2014[87]	Provox®2	Mean device life time 7.5 months (range 1 to 48 months).	210 patients (180 males, 30 females; mean age 58±11.9 years; range 37 to 83 years)
Messing et al. 2015[88]	Provox®2	Median lifespan : 92 days	15 patients (95% confidence interval
Yenigun et al 2015[32]	Provox®	mean lifespan: 17.1 months (range 1-36 months)	Retrospective 27 patients
Serra et al. 2015[33]	Provox® Provox®2 Provox® Vega™	median device life: Provox® 150 days, Provox®2 125 days, Provox® Vega 140 days	Retrospective 95 patients
Thylur et al 2016[34]	Provox®2 Provox® Vega™	mean (median) device life: Provox®2 115.6 (110) days, Provox® Vega™ 65.1 (80)days	Retrospective 21 patients 181 voice prostheses

Authors	Prosthesis	Device Life	Comments
Lewin et al. 2017[35]	Provox®2 (1096) Provox® Vega™ (44) Provox® ActiValve® (40) Provox® NiD™ (340) Blom-Singer Duckbill (4) Blom-Singer Low Pressure (255) Blom-Singer Indwelling (1383) Blom-Singer Indwelling Standard Enlarged Flange (205) Blom-Singer Advantage (251) Bivona Duckbill (10) Bivona Ultra Low (20)	Median device life per model: Provox® NiD™ 47 days, Provox®2 77 days, Provox® Vega™ 45 days, Provox® ActiValve® 161 days, Blom-Singer Duckbill 18 days, Blom-Singer Low Pressure 33 days, Blom-Singer Indwelling 59 days, Blom-Singer Indwelling Standard Enlarged Flange 42 days, Blom-Singer Advantage 67 days, Bivona Duckbill 7 days, Bivona Ultra Low 20 days.	Retrospective 390 patients 3648 voice prostheses
Friedlander et al. 2016[89]	Provox®2	Average: 56 days (Periprosthetice silicon collar inserted) Average: 32 days (Hyaluronic acid treatment) Average: 64 days (Combination of both)	
Serra et al. 2017[107]	Provox®2 (82) Provox® Vega™ (82)	Average lifetime: Provox®2: 146 days Provox® Vega™: 182 days	Multicenter prospective crossover study 82 patients
Robinson et al. 2017[108]	Provox® Vega™, PVPS	Average lifetime: intraoperative placed VP: 159.7 days delayed insertion: 24.5 days	Prospective study 24 patients (Intraoperative = 14, delayed = 10)
Mayo-Yáñez et al. 2018[109]	Provox®2 (192) Provox® Vega™ (214)	Median device lifetime per model: Provox 2: 74 days Provox Vega: 74 days	Retrospective case-crossover study 34 patients
Krishnamurthy et al. 2018[132]	Provox®2 Provox® Vega™	Mean lifetime: 16 months	Retrospective study 60 patients
Petersen et al. 2018[111]	Provox® Vega™ XtraSeal	Median lifetime; 68 days	Prospective study 13 patients

Authors	Prosthesis	Device Life	Comments
Petersen et al. 2019[110]	Provox®2 (1664) Provox® Vega™ (1136) Provox® ActiValve® Light (171) Strong (121)	Median device life per model: Provox 2: 63 days Vega: 66 days ActiValve light: 143 days ActiValve strong: 186 days	Retrospective cohort study 232 patients

Table 2. Overview of complications with Provox® prostheses (prosthesis and puncture related).

Authors	Prosthesis	Complications	Comments
Hilgers et al., 1990[4]	Provox®	Short-term fistula enlargement (8); hypertrophic scarring with fistula closure (3); surgical closure for intractable leakage (3).	79 patients, 67 converted from Groningen, 12 primary insertion
Hilgers et al., 1993[38]	Provox®	Temporary widened fistula 20.5% of patients; intractable leakage around due to enlarged fistula 3% (surgical closure); hypertrophic scarring/prolapse/infection 4.5%.	132 patients
Callanan et al., 1995[13]	Provox®	No major surgical complications. Overgrowth by esophageal mucosa solved with larger prosthesis (3); ingestion of prosthesis (1); leak around due to too long prosthesis pistoning (2)	28 patients
Van den Hoogen et al., 1996[14]	172 Provox® 220 Nijdam 453 Groningen (higher number of Groningen because this was the only one available up to 1990)	Hypertrophia and granulation most frequent complication. Provox®: Granulation 6%, Hypertrophia 4%, Infection 2% Groningen: Granulation 6%, Hypertrophia 4%, Infection 0% Nijdam: Granulation 12%, Hypertrophia 10%, Infection 0%	158 patients 845 consecutive placements
Toma et al., 1996[15]	Provox®	Fistula migration (4), esophageal mucosa overgrowth (3), prosthesis ingestion (1)	Cohort 31 patients
Ollas et al., 1996[16]	Provox® (95) Blom-Singer (4) Groningen (2)	Ingestion (2), extrusion (1)	101 patients

Authors	Prosthesis	Complications	Comments
De Carpentier et al., 1996[19]	Provox®	Leakage around requiring temp stenting with small catheter (7.7%), granulation formation (no % mentioned).	Retrospective 39 patients 81 prostheses
Slavicek et al., 1997[17]	Provox® (all secondary puncture)	Local inflammatory reaction in 28.1% resulting in extrusion or removal in 14.2%	53 patients 372 prostheses
Lacourreye et al., 1997[18]	Provox®	Early cellulites (1), granulation (6), puncture necrosis due to ill fitted prosthesis (1),	Retrospective (Nov 1990 –June 1994) 37 patients 100 prostheses
Cavalot et al., 1997[20]	Provox® (16) Blom-Singer (14)	Pooled for both types: Fistula dilation 10%, cellulitis 6.6%, extrusion 6.6%.	Prospective RCT Provox® vs Blom-Singer 30 patients, 16 Provox®, 14 Blom-Singer
Aust and McCaffrey, 1997[22]	Provox®	Partial retraction of prosthesis into esophagus due to too short prosthesis (2), granulation (1), cellulites (1)	Retrospective 21 patients 24 replacements in 13 patients
Nasser et al., 1997[23]	Provox®	Temporary leakage around (9 events) 'obstruction' (30 events) Porstheses migration (17 events)	Prospective Mar 1994 – Sep 1996 52 patients
De Racourt et al., 1998[21]	Provox® (majority but no exact numbers) Herrmann (until 1993) Traissac Blom-Singer	Pooled for all types: Enlarged fistula 16 patients, 37 episodes, 28 treated with shrinkage, 2 healed spontaneously, 7 surgical closures with repuncture in 4.	Retrospective, patients treated between Dec 1987 and Feb 1998, all with 5 year follow up. 62 patients
Baumann et al., 2000[25]	Provox® (1992-mid 1997) Provox®2 (mid 1997-1998)	Complications in 26 out of 478 used prostheses: mucosal overgrowth/embedding (14), aspiration/ingestion of prosthesis (3), aspiration pneumonia (3), local infection (4), granulation (2).	Prospective, 1992-1998 105 patients 478 prosthesis changes
Op de Coul et al., 2000[54]	Provox® Provox®2	Leakage around prosthesis not solved by downsizing in 3% of replacements, hypertrophic scarring in 7% of replacements, spontaneous loss of the device in 1% of 'replacements'.	Retrospective Nov 1988 – May 1999 318 patients 2700 replacements

Authors	Prosthesis	Complications	Comments
Balle et al., 2000[55]	Provox® Provox®2	Granulation tissue (14 patients), Infection (5)	Retrospective May 1989-May 1999 88 patients Conversion from Blom-Singer (non-indwelling) Duckbill to Provox®
Hotz et al., 2002[59]	Provox® Provox®2	Aspiration (1), ingestion (2), aspiration pneumonia (2), granulation (2)	Retrospective 1992-1998 82 patients
Fajdiga et al., 2002[60]	Provox®® Provox®2 Other (unnamed)	Pooled for all prostheses including unknown brand: Inflammation (12 events in 5 patients), prosthesis aspiration (4 events in 4 patients)	retrospective 32 patients 1998-2002
Cornu et al., 2003[27]	Provox®	22 adverse events in 16 patients: posterior displacement of prosthesis (5), anterior displacement of prosthesis (9), granulation (2), enlarged fistula (3), leakage adjacent to fistula (3).	Prospective 1995-1998 128 patients 63 replacements
Trussart et al., 2003[61]	Provox®/Provox®2 (93) Blom-Singer (73) Groningen (5) VoiceMaster (7)	Pooled for all types: Periprosthetic leakage (12: 11 treated with collagen and 1 with silastic sheet), granulomas (17.4%)	Retrospective long-term follow up (3 – 16 years)
Makitie et al., 2003[62]	Provox® Provox®2	In % of replacements: Granulation 9.2%, leakage around 7.2%, extrusion 0.5%	Retrospective 1992 - 2002 95 patients
Hancock et al., 2005[7]	Provox® NID™	Increased safety with increased flange resistance and safety medallion	Feasibility study in 15 patients, conversion from Blom-Singer Low Pressure
Bien and Okla, 2006[66]	Provox®2	Infection after 2ndary puncture 12.1%, partial extrusion 7.5%	Retrospective 2002-2004 106 patients 132 replacements
Calder et al., 2006[67]	Provox® Provox®2 Blom-Singer	Incomplete dataset and information in article 20% granulation	Retrospective 1993-2002 99 patients
Terada et al., 2007[69]	Provox®2	Oedema/necrosis around puncture (3 patients), granulation (3), aspiration pneumonia (2), leakage around (1).	Cohort 32 patients 2002-2004
Bilewicz et al., 2007[74]	Provox®2	Infection (N=7) Widening of fistula (N=4)	Prospective 39 TE speakers 10 esophageal speakers

Authors	Prosthesis	Complications	Comments
Ramalingam et al., 2007[76]	Provox®2 (21) Blom-Singer Low Pressure (20)	Less prosthesis related complications in Provox®	Prospective 41 patients, comparative
Soolsma et al., 2008[115]	Provox®ActiValve®	Esophageal pouch (N=4) Granulation (N=3) Extrusion (N=1)	Retrospective 42 patients with short device life time Long-term follow up
Gultekin et al., 2011[28]	Provox®	No complications neck dissection and postoperative radiotherapy	Retrospective 23 patients
Wierzchowska et al., 2011[82]	Provox®2	Granulation (n=11) Spontaneous falling out prosthesis (n=6) Leakage through or around prosthesis: 97.4%	Retrospective 76 patients
Lukinovic et al. 2012[85]	Provox®2	Early complication rate was 4.4%, and 10.9% of patients had late complications, with leakage being the most common problem.	Retrospective 91 patients
Cocuzza et al. 2014[29]	Provox®	Fistula related complications	Retrospective study 61 patients
Imre et al. 2013[30]	Provox®	Granulation (n=2, 4.2%), swallowing prosthesis (n=6 12.7%), Leakage around prosthesis (n=9 , 19.1%); mediastinitis (n=1, 3.1%), paraesophageal abscess (n=1, 3.1%)	Retrospective 47 male patients
Bozzo et al. 2014[141]	Provox®2	Mediastinal abscess and esophageal stricture	Case study 1 patient
Lorenz et al. 2015[146]	Provox®2 , ActiValve®	Fistula enlargement	Prospective cohort study 44 patients
Lorenz KJ. 2015[150]	Provox®, Provox® 2, Provox® Vega™, Provox® ActiValve®	Periprosthetic leakage: 35.7%. Substantial enlargement of the tracheo-oesophageal fistula: 12.5 % Granulation (n=43).	Retrospective, 1994 - 2013 32 patients,
Chaturvedi P, et al 2014[31]	Provox®	Central leak ; 43%, peri-prosthetic leakage: 57%	58 patients
Calkovsky et al 2015[148]	Provox®	Secondary voice prosthesis inserted through a T-E shunt. Day 6 post insertion the shunt decayed	Case study 1 patient
Serra et al 2015[33]	Provox®, Provox®2, Provox® Vega™	Overall complication rate was 13%: 90% pharyngocutaneous fistula, 5% bleeding, 5% other medical complications.	Retrospective 95 patients

Authors	Prosthesis	Complications	Comments
Lorenz et al.2016[147]	The type of Provox® voice prosthesis was not mentioned.	Rapid development of granulation tissue & incarceration of the prosthesis.	Case-study 2 patients
Fukushima et al. 2017[113]	Provox®2, Provox® Vega™, PVPS	Complication rate: 15.4% (20 patients) Local infection, leakage, stenosis, and spontaneous extrusion	Retrospective study 130 patients
Robinson et al. 2017	Provox® Vega™, PVPS	Postoperative complications: Intraoperative group 29% PCF (3), pulmonary embolism (1)Delayed group 20% PCF (2)	Prospective study 24 patients (Intraoperative = 14, delayed = 10)

Table 3. Overview of success rates with Provox® voice prostheses.

Authors	Prosthesis	Success rate	Comments
Hilgers et al., 1990[4]	Provox®	91% good voice quality 88% long-term users	79 patients 67 converted from Groningen 12 primary insertion
Hilgers et al., 1993[38]	Provox®	Fair-good voice 92%	132 patients
Callanan et al., 1995[13]	Provox®	Good speech intelligibility	28 patients
Toma et al., 1996[15]	Provox®	Long-term succes rate 88%	Cohort 31 patients
Ollas et al., 1996[16]	Provox® (95) Blom-Singer (4) Groningen (2)	95% of patients had fluent voice	63 patients that were alive at time of evaluation and used a voice prosthesis
Slavicek et al., 1997[17]	Provox® (all secondary puncture)	85% fluent speech	53 patients 372 prostheses
Cavalot et al., 1997[20]	Provox® (16) Blom-Singer (14)	96% success	Prospective RCT Provox® vs Blom-Singer 30 patients 16 Provox® 14 Blom-Singer
Aust and McCaffrey, 1997[22]	Provox®	88% success rate	Retrospective 21 patients 24 replacements in 13 patients
Nasser et al., 1997[23]	Provox®	78% good to excellent speech	Prospective Mar 1994 – Sep 1996 52 patients

Authors	Prosthesis	Success rate	Comments
Delsupehe et al., 1998[24]	Provox® Blom-Singer	Voice quality overall good and comparable for both types of prostheses	Prospective RCT 52 patients 113 prostheses
Chung et al., 1998[39]	Provox®	lower airflow resistance by 2.1kPa	Invitro and invivo study Provox®vs. Groningen
Ahmad et al., 2000[57]	Provox® Provox®2	82% good to average speech	Retrospective 1989-1999 100 patients converted from Blom-Singer non-indwelling to Provox®
Op de Coul et al., 2000[54]	Provox® Provox®2	95% long-term users 88% good to fair voice quality	Retrospective Nov 1988 – May 1999 318 patients 2700 replacements
Cornu et al., 2003[27]	Provox®	Good voice quality in 74%	Prospective 1995-1998 128 patients 63 replacements
Yamada et al., 2003[68]	Provox®2	86% successful speech	Cohort 15 patients
Makitie et al., 2003[62]	Provox® Provox®2	Good voice quality in 78%	Retrospective 1992 - 2002 95 patients
Ozkul et al., 2003[73]	Provox® (204) Blom-Singer (17) Groningen (5) Turvox (5)	92% success rate Intelligibility highest for Provox® prosthesis	Retrospective (?) 231 patients
Hancock et al., 2005[7]	Provox® NID™	Conversion successful in 14 out of 15 patients. Majority of patients prefers Provox® NID™ due to decreased speaking effort, increased speech quality, and increased safety	Feasibility study in 15 patients, conversion from Blom-Singer Low Pressure
Terada et al., 2007[69]	Provox®2	90.6% success rate	Cohort 2002-2004 32 patients
Gonzalez Poggioli et al., 2007[71]	Provox®2 (81) Blom-Singer (7) Herrmann (7) Groningen (1)	74% used prosthesis as usual means of communication	Retrospective Oct 2000-Dec 2005 96 patients
Bilewicz et al., 2007[74]	Provox®2	90% of patients acquired successful TE speech	Prospective 39 TE speakers 10 esophageal speakers
Ramalingam et al., 2007[76]	Provox®2 (21) Blom-Singer Low Pressure (20)	Better quality of voice production in Provox®2	Prospective 41 patient, comparative

Authors	Prosthesis	Success rate	Comments
Boscolo-Rizzo et al., 2008[75]	Until Sep 2001: Blom-Singer indwelling; From Sep 2001 : Provox®2	81.7% success rate on HRS scale. Success rate similar in primary and secondary puncture	Retrospective 93 speakers
Mastronikolis et al., 2008[80]	Provox®2 (12)	Good and intelligible speech in 80%.	Retrospective 12 patients.
Hancock et al.,2012[101]	Provox®Vega™	Patients prefer Provox® Vega over comparator device for cleaning and maintenance, voice quality and speaking effort.	Prospective randomized cross-over trial in 31 patients
Gultekin et al., 2010[28]	Provox®	neck dissection and postoperative radiotherapy no influence on speech	Retrospective 23 patients
Hilgers et al.,2010[99]	Provox®Vega™	Speech better and speaking effort lower with larger diameter prostheses.	Prospective feasibility study; short term (2/3 weeks)
Ward et al,2011[102]	Provox®Vega™	Voice perceived to be better with Provox® Vega by clinicians and patients	Prospective randomized cross-over trial in 31 patients
Lukinovic et al. 2012[85]	Provox®2	75.8% of all patients had successful rehabilitation	Retrospective, 91 patients
Polat B, et al 2014[36]	Provox®	Voice prosthesis improved quality of life, self-esteem and sexual function. Depression and anxiety decreased.	Uncontrolled single-arm study 30 patients
Dabholkar JP et al 2015[47]	Provox®	70% developed a good voice, 30% an average voice.	Prospective nonrandomized cross-sectional observational study 30 patients
Serra et al 2015[33]	Provox®, Provox® 2, Provox® Vega™	success rate 87.5 %, 84% primary TEP, 91% secondary TEP	Retrospective 95 patients
Yenigun et al 2015[32]	Provox	Fluent and understandable speech in 85%	Retrospective 27 patients
Timmermans et al. 2016[117]	Provox® ActiValve®	The fluoroplastic material of Provox® ActiValve® seems insusceptible to destruction by Candida	Microbiological study 33 voice prostheses

Authors	Prosthesis	Success rate	Comments
Serra et al. 2017[107]	Provox®2 (82) Provox® Vega™ (82)	The perceptual voice data showed a better rating across all parameters for the Provox Vega in relation to Provox 2.	Multicenter prospective crossover study 82 patients
Fukushima et al. 2017[113]	Provox®2, Provox® Vega™, PVPS	Satisfying communication outcome with Provox insertion: 78.4% (102)	Retrospective study 130 patients
Robinson et al. 2017[108]	Provox® Vega™, PVPS	Intraoperative placement with Provox Vega: earlier voicing (13.2 vs 17.6 days), less changes due to resizing (8% vs 80%), reduced hospital stay (17.2 vs 24.5 days) and cost savings.	Prospective study 24 patients (Intraoperative = 14, delayed = 10)
Leonhard et al. 2017[118]	Provox® ActiValve® (Provox®2 , Provox® Vega™, Blom Singer Advantage, Phonax)	Provox® ActiValve® (and Blom Singer Advantage) showed significantly less surface biofilm formation.	In vitro study 12 valve flaps/vp

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