The Knife or the Pill in the Long-Term Treatment of Gastroesophageal Reflux Disease?

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Gastroesophageal reflux disease (GERD) is a common condition, and it is now generally recognized that modern medical therapy allows the physician to both heal the esophagitis and relieve the patients from troublesome symptoms such as heartburn, acid regurgitation and disabling chest pain. In addition, long-term therapy with potent acid inhibitory drugs can maintain these patients in clinical remission. The indications for antireflux surgery and long-term medical therapy have developed and changed with time but are today essentially similar, and in fact, it can be hypothesized that the outcome of a short-term “therapeutic trials” with the proton pump inhibitor would be a useful clinical tool, not only as a diagnostic test for the disease but also in the selection process before referring the patient to antireflux surgery. Antireflux surgery is designed to improve the function of the antireflux barrier by reconstructing the physiology of the gastroesophageal junction. Studies have shown that a fundoplication procedure improves the strength and length of the lower esophageal sphincter and also restitutes the flutter valve mechanism. However, since gastroesophageal reflux disease is a common disorder, it is impossible for every patient to be attended by an expert surgeon, and this might be one important reason for the sometimes poor results presented after surgical treatment.

When the question arises about which type of long-term therapy should be chosen in each clinical situation, this situation should also partly be influenced by some epidemiological information. If we assume that we expose a hypothetical group of 100 patients with symptomatic, chronic severe reflux disease, also presenting endoscopic evidence of esophagitis of varying severity, available clinical information would suggest that only 25 can be considered suitable for antireflux surgery, depending on the frequently associated complicating medical disorders and the age distribution of the actual patient population. Therefore, it deserves to be emphasized that the majority of patients with complicated reflux disease are not fit for surgery and should consequently be managed medically. For younger patients with disabling GERD, antireflux surgery is still the gold standard and obviously very cost effective.

INTRODUCTION

Recent advances in the medical treatment of gastroesophageal reflux disease (GERD) now allows the physicians to both heal acute episodes of esophagitis and maintain these patients in clinical remission [1]. It is also generally accepted that medical therapy can be used as a long-term maintenance therapy and may also be a legitimate alternative to surgery for the management of severe, long-standing GERD. A comprehensive assessment of the relative merits of the different treatment options requires, however, generally accepted criteria for the assessments of the severity of GERD with respect both to symptoms and/or the presence of complications. In the medical literature,

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Abbreviations: GERD, gastroesophageal reflux disease.
there is a general agreement on the designs of studies to be used in clinical science, allowing the assessment of treatment outcomes (such as endoscopic healing and symptom relief) and forming the basis of an objective comparison between different drug regimens. A corresponding consensus on the design of clinical trials over the efficacy of antireflux surgery is unfortunately not available. Despite these methodological obstacles, which complicate a comprehensive, comparative analysis, the aim of the present review is to present the merits of medical and surgical therapy per se and to put these therapeutic alternatives in the context of the epidemiology, natural history and complications of the disease.

THE EFFICACY OF MEDICAL TREATMENT OF GERD

The main priority of any treatment based on a proper diagnosis of GERD is to control symptoms arising directly from esophageal mucosal contact with refluxed contents of predominantly gastric nature [2]. Control of esophagitis produced by peptic injury to the esophageal mucosa is a more long-term aim of therapy. When assessing different clinical trials, endoscopic healing rates have been used [3] as an estimate of efficacy, also with the addition of data on complete symptom relief (resolution) of major reflux symptoms. The three general classes of medication used in similar therapy of reflux esophagitis are antisecretory drugs, prokinetic agents and mucosal coating compounds.

A relationship exists between the degree of inhibition of gastric acid secretion induced by various drugs and the subsequent capacity of these to heal the esophagitis. This correlation is explained by the linear relationship between the per cent enhancement of gastric pH and the percentage of time during which the intra-esophageal pH is observed to be above 4 [4, 5]. Consequently, the clinical experience with the most effective acid inhibitory drugs, i.e., proton pump inhibitors, reveals that there are essentially very few patients resistant to this type of medical treatment (Table 1) [6-18].

| Study drug       | n   | Endoscopic remission (%) | Symptom free (%) |
|------------------|-----|--------------------------|------------------|
| Ome (20 mg)      | 361 | 82.4                     | 80.8             |
| Ome (10 mg)      | 225 | 71.9                     | 64.1             |
| Ran (150 mg x 2) | 179 | 52.3                     | 52.0             |
| Placebo          | 146 | 10.6                     | 20.7             |

The success of short-term medical therapy in patients with reflux esophagitis essentially depends on two factors: one is the pretreatment severity of the erosive and/or ulcerative lesions in the esophagus and the other is the choice of drug therapy. However, irrespective of the type of initial drug therapy, patients will relapse frequently after cessation of treatment. The slope of this relapse curve might be dependent on the pretreatment severity of the esophagitis as well, but other factors of clinical importance may also be operating.

The fact that the slope of the relapse curve is very steep suggests that reflux esophagitis is, in many cases, a chronic disease, and the esophagitis with associated symptoms will recur irrespective of the type of initial healing therapy. In fact, in patients with esophagitis, the relapse rate is as high as 50-80 percent within the first 6-12 months after stopping treatment. A low-dose maintenance treatment with H2-receptor antagonists
(half the dose required to heal the peptic lesions), a therapeutic principle which is effective in preventing recurrent peptic ulcer disease, has not proven to be effective in reflux esophagitis [19, 20]. On the other hand, by use of higher and more frequent doses of H₂-receptor antagonists, relapses can be prevented. The number of studies reporting an overwhelming efficacy of omeprazole (the first synthesized proton pump inhibitor) as a maintenance therapy for reflux esophagitis is increasing (Table 1). Even in patients with more severe grades of esophagitis, 20 mg of omeprazole daily has proven adequate in all but a minority of patients.

The eventual role of prokinetic agents (the most widely used being cisapride) seems to be in patients with milder forms of the disease, but it should be noted that a high placebo remission rate has been observed in these trials (Table 2) [21-23]. The initial severity of the endoscopic lesions, as well as the type of therapy chosen, has a significant impact on the number of patients who could be kept in remission during maintenance long-term therapy.

Table 2. Proportion of GERD patients kept in endoscopic and clinical remission in trials evaluating the long-term efficacy of cisapride (cis.) [21, 22, 23].

| Endoscopic grading | Study drug         | n   | Endoscopic healing (%) | Symptom free (%) |
|--------------------|--------------------|-----|------------------------|------------------|
| ≥ 2                | Cis. 10 mg x 2     | 37  | 80                     | 81               |
| ≥ 2                | Placebo            | 43  | 61                     | 63               |
| All                | Cis. 20 mg x 2     | 147 | 58                     | 45               |
| All                | Placebo            | 151 | 47                     | 21               |
| 1                  | Cis. 20 mg x 2     | 51  | 73                     | No data          |
| 1                  | Placebo            | 51  | 53                     | No data          |
| All                | Cis. 20 mg noct    | 151 | 68                     | 56               |
| All                | Cis. 10 mg x 2     | 149 | 66                     | 63               |
| All                | Placebo            | 143 | 49                     | 42               |
| 1                  | Cis. 20 mg noct    | 55  | 90                     | No data          |
| 1                  | Cis. 10 mg x 2     | 60  | 77                     | No data          |
| 1                  | Placebo            | 53  | 58                     | No data          |

Oesophageal complications of reflux esophagitis consist primarily of bleeding, ulceration, formation of stricture and the development of columnar lined esophageal mucosa (Barrett's esophagus). Peptic stricture and Barrett's esophagus are not only the major but also the most common serious complications of the disease [24]. The clinical problems related to these manifestations are highly significant, and in patients with peptic stricture, the resulting dysphagia can be a major disability that causes nutritional problems. Dilatation of a stricture exposes the patients to a small but significant risk of esophageal perforation. Barrett's esophagus per se rarely causes morbidity but carries a significant risk of developing esophageal adenocarcinoma with its attended morbidity and mortality. The primary, long-term aim of medical therapy for patients with peptic stricture and Barrett's esophagus is the abolition of reflux symptoms and prevention of immediate risk of recurrence or progression of complications. Prevention of progression is thought to be achieved by healing of erosive or ulcerative lesions. The need for repeated dilatation in patients with peptic stricture is considerably lower in those undergoing fundoplications than in those treated conservatively (i.e., with antacid or H₂-receptor antagonists) [24]. In fact, no prospective, controlled, randomized study has been presented.
to show a reduction in repeat dilatation with the use of $H_2$-blockers [25, 26]. Omeprazole has the potential to produce clinical responses similar to that seen after successful antireflux surgery due to its effect on acid reflux into the esophagus. Results from on-going trials with omeprazole in patients with peptic strictures have presented very promising preliminary results, showing that the clinical aims can be fulfilled [27, 28].

When studying patients with Barrett’s esophagus and the clinical response to different therapeutic interventions, a clear distinction must be made between healing of the esophagitis and regression of the metaplastic epithelium. Initial healing of the erosive and/or ulcerative lesions in the squamous epithelium has been accomplished with high doses of $H_2$-receptor antagonist therapy, but such a regimen is not an attractive long-term therapeutic option for the prevention of relapse of reflux symptoms and esophagitis due to the need for very high doses and frequent dosing. Recently, a number of case reports have been published and demonstrated remarkable symptomatic response in patients with Barrett’s esophagus when treated with omeprazole [24]. Medical therapy has not, so far, been shown to induce any major and significant changes in the length of the columnar lined segment [29, 30]. In addition, it should always be born in mind that patients with Barrett’s esophagus, in whom reflux is controlled either medically or surgically, must undergo regular surveillance for the development of dysplastic or neoplastic lesions in the metaplastic epithelium [31].

“ALKALINE REFLUX”?

The role of acid and pepsin in the pathogenesis of GERD and its complications is well documented, but the importance of refluxed alkaline duodenal contents is a controversial issue. Animal studies have suggested that bile acids are injurious to the esophageal mucosa [32, 33], and the following circumstantial, clinical evidence for the role of these compounds in the pathogenesis of reflux complications have been obtained from human studies: a) bile reflux causes heartburn; b) esophagitis can occur in the presence of atrophic gastritis associated with pernicious anemia and after total gastrectomy; and c) increased amounts of duodenogastric reflux have been reported in patients with esophagitis compared to those without esophagitis, and particularly in those with severe complications of the disease such as strictures and columnar lined esophagus [34, 35]. During ambulatory 24-hr pH-monitoring, rises in pH above 7 occur infrequently and have been alleged to be caused by duodenogastric reflux. However, recent reports have suggested that these pH-raises are more likely the result of local factors in the esophagus [36] such as bicarbonate production, swallowed saliva, etc., and not due to pure alkaline gastroesophageal reflux as initially suggested [34, 35, 37]. On the other hand, conjugated bile acids can be detected in the gastric juice in 75 percent of reflux patients, particularly when collected at night, but on the other hand, only two percent of esophageal aspirates contained concentrations of these compounds, which would increase the esophageal mucosal permeability. Taken altogether, it seems as if hydrogen ions and pepsin, probably acting synergistically, are the most important components of the refluxate with the potential to cause clinically relevant esophageal mucosal damage. In addition, reduction in acid output and consequent elimination of acid exposure in the esophagus also concurrently reduced the alkaline refluxate in the esophagus. Thus, different arguments have been raised as to the type of therapy to be recommended in patients with alleged duodenogastroesophageal reflux (i.e., antireflux surgery and the creation of a competent antireflux mechanism or medical therapy in the form of potent acid inhibition). One way of reaching an opinion on this issue is to consider the efficacy by which these different therapeutic principles have been documented to induce a regression of established Barrett’s epithelium or resolution of strictures. In fact, a reasonably-well established, but
still unpredictable, regression of the columnar lined mucosa seems to occur at a similarly small frequency irrespective of the type of therapy instituted [29-30, 39-40].

POTENTIAL SIDE-EFFECTS

All of the drugs that might be used for long-term maintenance therapy have proved to be remarkably safe in short- and intermediate long-term use. However, the theoretical disadvantages associated with long-term medical therapy may be grouped into three classes:

1. Side-effects that are specific for the drug itself
2. Side-effects that are secondary to long-term suppression of acid secretion.
3. Effects attributable to suboptimal treatment of the underlying gastroesophageal reflux disease.

Although infrequently seen, cisapride occasionally may produce intolerable diarrhea, necessitating withdrawal of therapy. H2-receptor antagonists have a very good safety record even when used long-term [41]. Omeprazole has a very low incidence of side-effects quite comparable to that of H2-blockers [42]. During the early experience with H2-blockers, and now also with the clinical use of proton pump inhibitors, it has been argued that the use of similar substances might cause severe diarrhea. This is seen particularly in underdeveloped countries due to superimposed enteric infections, allegedly caused by the lack of acid in the stomach. The wide-spread clinical use of acid inhibitory drugs, including omeprazole, all over the world has not confirmed this hypothetical potential adverse consequence of the use of similar drugs.

Bacterial overgrowth in the stomach, nitrosamine formation, hypergastrinaemia and enterochromaffin-like cell formation are all potential hazards, which may follow long-term potent acid suppression. The present state of knowledge does not, however, support the notion that omeprazole or the H2-receptor antagonists currently available have any of these serious long-term side-effects. Proton pump inhibitors produce a slight to moderate hypergastrinaemia during acute treatment, which remains during continued therapy [43]. Follow-up of patients who have taken omeprazole for five years has shown a slight increase in mean argyrophilic cell volume density, which may be influenced both by the natural development of chronic gastritis but also by the enhanced gastrin release. However, no dysplastic or neoplastic endocrine cell lesions have been recorded [44].

It has been argued that long-term medical maintenance therapy may abolish symptoms without healing esophagitis and thus permit the progression of the asymptomatic esophageal lesions, to the extent that severe complications may occur in the form of stricture, Barrett’s esophagus and ultimately carcinoma. Few if any data, however, support this hypothesis, and on the contrary, good symptom relief with potent antisecretory agents seems to be closely associated with the resolution of the esophageal lesions [45]. It must, however, be remembered that a comprehensive and really firm view on the frequency of side-effects on really long-term medical therapy has to wait at least another five years, when the data from the surveillance program currently in clinical use have been analyzed.

ANTIREFLUX SURGERY

Antireflux surgery is designed to improve the function of the gastroesophageal junction and to provide the GERD-patients complete relief of all symptoms and complications of reflux disease, all of which occur secondary to deficiencies in the reflux preventing barrier located in that area [46]. Ideally, reconstruction of the physiology of the gastroesophageal junction should also permit the patient to swallow normally, belch to relief distension, but hardly to vomit. A major effect of fundoplication operations has been
shown to be a substantial reduction in the number of transient lower esophageal sphincter relaxations [47]. In addition, the proportion of these relaxations accompanied by reflux is decreased, as well as a concomitant increase in the residual pressure at the gastroesophageal junction during sphincter relaxation [47]. This is probably another additional important mechanism to prevent reflux, especially in cases with severe complications of the disease [48]. Previous data have repeatedly shown that fundoplication operations restrain the lower esophageal sphincter relaxations during water swallows by what seems to be a purely mechanical effect [49-54]. The mechanism by which funduplications interfere with the triggering of transient sphincter relaxations has, however, yet to be defined. The prevention of reflux during complete lower esophageal sphincter relaxation, even after a fundoplication, suggests that there are other effects of fundoplication on sphincter function separate from that of a simple external cuff. In vitro and in vivo studies have shown that the sphincter length contributes to sphincter competence and that fundoplication increases the length of the sphincter exposed to intra-abdominal pressure [55]. Undoubtedly, these operations also produce a simple, one-way mechanical flap or flutter valve.

At the time of Allison’s original report [56], surgical attention was on the anatomical defect in the hiatus forming the hernia rather than the problem of a physiological defect of incompetence in the reflux preventing mechanisms within the gastroesophageal junction. Consequently, operations that anatomically repaired only the hiatus and the hernia were not successful [57]. Nissen discovered that a fundic wrap prevented reflux when he studied a patient many years after partial esophagectomy [58]. Fundoplication has subsequently become the most widely used form of antireflux surgery, and the efficacy has been established by clinical and endoscopic follow-up and also by esophageal 24-hr pH-monitoring [46, 59]. Over the last three decades, a number of modifications of the original fundoplication operation have evolved, but not every surgeon using the actual technique is as satisfied with the clinical outcome as the originator [60, 61]. Gastroesophageal reflux disease is such a common condition that it is impossible for every patient to be attended by an expert, and this might be one important reason for some of the poor results. It is clear that the overwhelming majority of studies report good to excellent results in the order of 80 percent or better. To obtain a comprehensive view on the clinical outcome of different antireflux procedures, data must be compiled from controlled, clinical trials. By doing that, it can be concluded that obvious clinical differences in the efficacy between different antireflux procedures seem not to be prevailing when the outcome is judged with regard to the cumulative GERD relapse rate (evaluated endoscopically and/or symptomatically) [53, 62-68] (Table 3). Excellent control of gastroesophageal reflux symptoms can be obtained with a total fundic wrap, a 270° fundoplication, 180° fundoplication or Hill posterior gastropexi, provided that each operation involves the reduction of hiatal hernia coupled with the construction of the valve mechanism to re-establish gastroesophageal competence. It must be emphasized that these success rates can and should be achieved with negligible mortality and morbidity. The problem is, however that published results usually represent the best results in the field of antireflux surgery, and the local level of expertise can vary considerably.

Accordingly, it is reasonable to propose that antireflux surgery should be performed only in centers, where the expertise has been assembled in the management of gastroesophageal reflux disease as well as in the essential diagnostic facilities. Data are now accumulating to show that the outcome after laparoscopic fundoplication is as advantageous as that following open surgery. Long-term data after the former procedures are,
Table 3. The clinical outcome of different antireflux procedures when evaluated in prospective, controlled, randomized clinical trials.

| References          | Follow-up period | Procedure                  | Excellent to good results (%) | Failure rate (%) |
|---------------------|------------------|----------------------------|-------------------------------|-----------------|
| Washer et al. (1984)| 5 years          | Nissen (360)               | 65%                          | 20%             |
|                     |                  | Roux-en-Y                  | 91%                          | 41%             |
| DeMeester et al. (1974) | 30 - 696 days   | Hill                       | 47%                          | 53%             |
|                     |                  | Nissen (360)               | 100%                         | 0%              |
|                     |                  | Belsey (270)               | 80%                          | 27%             |
| Gear et al. (1984)  | 1-2 years        | Angelchik                  | 96%                          | 4%              |
|                     |                  | Nissen (360)               | 81%                          | 19%             |
| Stuart et al. (1989)| 38 months        | Angelchik                  | 77%                          | 23%             |
|                     |                  | Nissen (360)               | 94%                          | 6%              |
| Hill et al. (1994)  | 7 years          | Angelchik                  | 77%                          | 23%             |
|                     |                  | Nissen-Rossetti (360)      | 88%                          | 8%              |
| Kmiot et al. (1991) | 3-24 months      | Angelchik                  | 60-72%                       | 28%             |
|                     |                  | Nissen                     | 85-88%                       | 12%             |
| Thor, Silander (1989)| 5 years          | Nissen (360)               | 67%                          | 25%             |
|                     |                  | Toupet (180-200)           | 95%                          | 0%              |
| Lundell et al. (1991)| 6 months        | Nissen-Rossetti (360)      | 95%                          | 3%              |
|                     |                  | Toupet (180-200)           | 95%                          | 3%              |
| Walther et al. (1992)| 13 months       | Nissen (360)               | 92%                          | 8%              |
|                     |                  | Lind (300)                 | 96%                          | 4%              |
| Janssen et al. (1993)| 12 months       | Nissen (360)               | 90%                          | 0%              |
|                     |                  | Lig. teres gastropexi      | 40%                          | 60%             |
| Lundell et al. (1994)| 4 years         | Nissen-Rossetti (360)      | 96%                          | 11%             |
|                     |                  | Toupet (180-200)           | 94%                          | 6%              |

however, warranted [69-70]. A technique that largely eliminates the inter-surgeon variation in technique is the introduction of the Angelchik prosthesis. This operation has been shown to be an effective operation for controlling reflux. In the controlled clinical trials presented so far, this procedure has been shown to be as effective as Nissen fundoplication in preventing reflux symptoms [63-65]. The disadvantages with the prosthesis are the risk of dysphagia and migration of the prosthesis [71]. Consequently, this technique is not to be recommended. It should always be born in mind that adequate and sustained reflux control can essentially always be accomplished by an experienced surgeon taking the advantage of wrapping the mobile gastric fundus around the distal esophagus.

Unless there is a clear indication for a thoracic approach, the choice of the abdominal route is to be preferred [46, 59]. The thoracic procedure takes twice as long to accomplish as a transabdominal fundoplication, and major postoperative problems seem to be more frequent and are specific for the repair such as post-thoracotomy pain.

Although antireflux surgery is generally very effective in controlling gastroesophageal reflux, some failures are proven unavoidable. Persistent postprandial adverse
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Symptoms (in the form of dysphagia, inability to belch and vomit, postprandial fullness, bloating and pain and sometimes socially embarrassing flatulence) can mar an otherwise excellent result in a small but significant group of patients after similar procedures [72-73]. The frequency by which these postfundoplication symptoms have been reported varies considerably between series, from as low zero percent up to 40 percent. Dysphagia is frequently reported during the early postoperative period but vanishes with the passage of time. Except for dysphagia, these complaints have been assembled under the clinical syndrome named “gas bloat.” It should, however, be emphasized that patients very often rate their postprandial symptoms as of doubtful clinical significance and very much less than the preoperative reflux symptoms [74]. Another significant clinical observation is that postfundoplication symptoms, as well as gas bloat symptoms, improve with the passage of time. Some clinical studies even report an impressive number of patients being able to vomit postoperatively, especially when interviewed after many years [75-78]. Similar clinical information should, however, cause concern regarding an eventual disruption of the wrap rather than an example of subsidence of complaints with the passage of time. Since we lack effective treatment of established, severe postfundoplication symptoms, prevention is a primary concern. A number of technical considerations have been focused on and alleged to counteract some of these problems, but it must be concluded, based on data from controlled, randomized clinical trials, that, as yet, no significant differences with regard to postfundoplication symptoms have been firmly established among different antireflux procedures. There is a widespread consensus, however, among experienced surgeons that if a complete (360°) wrap is done it has to be both floppy and short, which means that the gastric fundus has to be widely mobilized and the fundoplication done only 1 cm long [79-81]. However, a tendency has been reported in some trials that semifundoplication procedures seem to be associated with less troublesome complaints [53, 67].

Failure of the floppy fundoplication to control reflux symptoms occurs in four to nine percent of patients. There are reports with a considerably higher failure rate, and it is important to emphasize that essentially all failures occur early in the postoperative period, indicating the importance of adhering to technical details [82-88]. Ideally, follow-up should be carried out by an independent assessor or by means of a detailed performa and by objective data. Postoperative endoscopic examination is valuable, and the follow-up period should last at least five years. Surgeons, who undertake this surgery need to agree on standardized operative methods and objective criteria to define success, thereby allowing an agreement on classification of anatomical, pathological and endoscopic features of the disease and the consequences of adequate long-term control of the disease [89]. Studies have been published in which conventional medical therapy has been compared to antireflux surgery [90-92]. Recently, Spechler and co-workers [93] confirmed the superiority of antireflux surgery over traditional medical therapy to treat complicated GERD in older male veterans. Further studies, however, are needed to address this issue, not only in women and non-veteran populations, and available data would thus suggest the importance of antireflux surgery as still occupying the position as being the gold standard for long-term treatment of GERD. In this context, it is relevant to point out that the inclusion period of a trial comparing antireflux surgery with long-term omeprazole treatment has just been completed, and the outcome of this trial will form a comprehensive basis for future decision-making processes when dealing with the long-term therapeutic strategy of GERD. A clear assessment of the role of surgery in relation to medical therapy can come only from similar trials, in which entry and outcome criteria are strictly defined, the study population is sufficiently large and the patients are followed for at least five years. This is especially true, since available data in...
the literature contain results from studies comparing the outcome of medical and surgical treatment, where the medical alternative is far from optimal and not updated.

The indications for antireflux surgery today are: patients with long-standing, well-established, chronic gastroesophageal reflux disease requiring frequent intermittent and/or continuous medical therapy to control symptoms and/or the esophageal lesions. Severe complications in the form of strictures, Barrett’s esophagus and respiratory complications are generally approved of as being indications for antireflux surgery. Frequent relapses in patients with a well-established GERD are also the well-established indication for long-term medical maintenance therapy. This means that the indications for long-term medical and surgical therapy are essentially the same. In fact, it can be argued that an adequate clinical response to a proton pump inhibitor is an important prerequisite for a successful outcome after antireflux surgery, thereby taking the advantage of the outcome of the short-term therapeutic effect of proton pump inhibitors as being a useful diagnostic test for the disease [93]. This hypothesis must, however, be proven in future clinical trials.

**COMPARATIVE TRIALS**

The only scientifically accepted way of establishing an eventual advantage of one therapeutic principle over another is to carry out a comparative, randomized clinical trial. There are a number of obstacles that make the design and logistics of similar trials complicated. However, some studies have already been completed, and the short-term outcome of these clearly favors the surgical alternative [90, 91, 92]. It is interesting to note that in the Veteran Administration study [94], the total frequency of complaints was fairly similar in the surgical and medical treatment groups. In the medical treatment arm, the complaints of reflux symptoms dominated, whereas in the surgical group, postfundoplication symptoms of varying severity seem to be most predominating. Unfortunately for the clinical decision process of today and the near future, the medical therapy applied in the actual studies is not relevant. A trial comparing proton pump inhibitors and antireflux surgery represents the treatment options of today and tomorrow.

**EPIDEMIOLOGICAL SUPPORT IN THE PROCESS OF DECIDING BETWEEN THE KNIFE AND THE PILL**

National incidence and prevalence data have to be estimated from extensive interview protocols and consequently subjected to either over- or underreporting [93-95]. The percentage of patients with reflux symptoms found to have esophagitis (and therefore having a firm diagnosis) at endoscopy varies from 20-75 percent depending on the selection process applied to the study population [96-97]. We need to examine large endoscopic series of patients to assess the true prevalence of esophagitis in the general gastroenterological practice. It seems, however, as if esophagitis is seen at least as frequently as duodenal and gastric ulcers in the endoscopy suite, but the GERD is seldom a cause of death (except postoperatively and postinterventionally) and rarely causes hospital admission. According to Brunnen and co-workers [98], the annual mortality rate from severe esophagitis was 0.1/100,000 from 1951-1967, but when the operative mortality was considered, the total annual mortality rate rose to 0.16/100,000. In adults, the incidence of reflux symptoms and esophagitis increases with age, and the disease severity seems also to increase with age. More than half of the patients with Barrett’s esophagus who present themselves to an endoscopy unit are over 70 years of age, and up to two-thirds of them have reported to have another reflux complication as well [99]. Among patients with endoscopically verified esophagitis, a considerable number have concomitant complicating medical disorders, which sometimes may call for greater attention than
the GERD itself. It can be theoretically calculated that from a hypothetical group of 100 patients with symptomatic and endoscopically diagnosed GERD only 25 can be considered suitable for antireflux surgery depending on the different clinical considerations as detailed above. Apparently, the great majority of patients with complicated reflux disease are not fit for surgery and should, thus, only be managed medically. However, for patients who do not present an increased surgical risk and who also have symptomatic, severe GERD with or without esophagitis, antireflux surgery is still the gold standard to which all future alternative therapeutic regimens should be compared. Provided that antireflux surgery is performed with an optimal technique, the actual operative risk of the patients should be the factor that determines the choice of therapy. The long-term consequences of antireflux surgery on the quality of life in patients with GERD is impressive, and in addition to that, the advantageous cost-effective ratio of surgery is obvious. In fact, the cost of a laparoscopic fundoplication corresponds roughly to 2.5 years of maintenance medical therapy [100].

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