

**Ten-year trend of the cumulative *Helicobacter pylori* eradication rate for the “Japanese eradication strategy”**

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## **Abstract**

Background/Aims : In Japan, a systematic eradication strategy for *H. pylori* has been constructed. Which is PPI/AC (PPI, amoxicillin and clarithromycin) therapy as the first-line regimen and PPI/AM (PPI, amoxicillin and metronidazole) therapy as the second-line regimen. The cumulative rate of *H. pylori* eradication has not been reported. Therefore, we investigated the annual and cumulative eradication rate to verify the efficacy of the “Japanese eradication strategy”.

Methods : Patients who received first-line PPI/AC and, if necessary, second-line therapy with PPI/AM between 2000 and 2009 were retrospectively analyzed. The annual cumulative eradication rate was calculated. Data were subjected to ITT analysis.

Results : PPI/AC was administered to 1973 patients (male n=1162, female n=811; mean age 55.8 y, range 15-87), and 250 patients received PPI/AM. Eradication rate for the PPI/AC was 65.3%, and it gradually but significantly decreased in 10 years ( $p<0.05$ ).

For the PPI/AM, the eradication rate was 84.0%, with no change in the annual eradication rate. Regarding the cumulative eradication rate, 76.0% in ITT and 98.4% in PP, respectively, which provided a consistent annual eradication rate without decreases in effectiveness.

Conclusion : Although the eradication rate for first-line PPI/AC decreased over time,

“Japanese eradication strategy” provided a sufficient eradication rate.

## **Introduction**

It has been said that *H. pylori* infection not only causes gastritis, peptic ulcer, and gastric cancer, but also has a relationship with idiopathic thrombocytopenic purpura, extranodal marginal zone lymphoma, and other conditions. In Japan, a systematic eradication strategy for *H. pylori* was constructed (1). Patients are administered PPI/AC (PPI, amoxicillin and clarithromycin) therapy as the first-line regimen, and, if the initial treatment has failed, PPI/AM (PPI, amoxicillin and metronidazole) therapy is prescribed as the second-line regimen. Some reports have indicated that the efficacy of PPI/AC first-line therapy has gradually decreased in recent years while the PPI/AM second-line therapy continues to provide sufficient results (2)(3)(4). While there have been many reports about each therapy in Japan, there has been no report of the cumulative *H. pylori* eradication rate by those successive therapies in Japan, which would practically reflect the clinical side of *H. pylori* eradication treatment. In this study, we investigated the cumulative eradication rate to verify the efficacy of the “Japanese eradication strategy”.

## Methods

Study subjects were those diagnosed as having *H. pylori* infection by the urea breath test, serum *H. pylori* immunoglobulin G, *H. pylori* antigen in stool, rapid urease test, or histopathological examination and received first-line PPI/AC therapy (lansoprazole 30 mg, omeprazole 20 mg or rabeprazole 10 mg, amoxicillin 750 mg and clarithromycin 200 mg or 400 mg twice a day for 7 days) in our department between January 2000 and December 2009 (Figure 1). Therapeutic results were mainly judged by the urea breath test one month or later after therapy. Patients who did not receive this evaluation were considered lost to follow up. Some of those experiencing failure of the first-line therapy received PPI/AM (lansoprazole 30 mg, omeprazole 20 mg or rabeprazole 10 mg, amoxicillin 750 mg and metronidazole 250 mg twice a day for 7 days) as second-line therapy. Success was judged the same as for first-line therapy. In this retrospective study, data on treatment and results were extracted from each patient's record and the annual eradication rate was calculated for 10 years for first-line therapy only, second-line therapy only, and the cumulative rate with success of second-line therapy added to that of first-line therapy. These data were subjected to intention to treat (ITT) analysis, and the cumulative eradication rate was determined by per protocol (PP) analysis. With ITT analysis, all enrolled patients were included, and patients who were

lost to follow up and therefore did not undergo an evaluation after therapy were regarded as “failed to be cured”. With PP analysis, patients who did not undergo the evaluation after therapy were excluded from the analysis. Statistical analysis was evaluated by the Cochran-Armitage trend test. P values less than 0.05 were considered statistically significant.

## Results

PPI/AC first-line therapy was administered to 1973 patients (male n=1162, female n=811; mean age 55.8 y, range 15-87) and 250 patients (male n=125, female n=125; mean age 55.0 y, range 22-85) received PPI/AM second-line therapy during the study period (Table). Patients who received other regime than 7days PPI/AM were considered as lost to follow up before second line therapy. As to the background disease, 20.1% had gastric ulcer, 22.7% had duodenal ulcer, 9.0% had gastro-duodenal ulcer, and 35.4% had only gastritis.

Eradication rate for the PPI/AC regimen was 65.3%. Eradication rate for the first therapy gradually but significantly decreased over the 10 years ( $p<0.05$ ) (Figure 2).

Among the frequent side effects were soft stool and diarrhea (7.9%), rash (1.0%), abdominal pain (0.5%), and nausea (0.5%). Five of those with diarrhea experienced hemorrhage. There were no severe adverse effects.

For the PPI/AM second-line therapy, the eradication rate was 84.0% with no changes in the annual eradication rate. Side effects were diarrhea or soft stool (6.8%), stomatitis (2.0%), and various skin problems (1.6%). As with the first-line therapy, there were no severe adverse effects.

Lansoprazole was the most frequently prescribed PPI in both first- and second-line therapies (first-line: 81.2%, second-line: 53.6%) (Figure 3,4). However, the eradication rate did not differ according to the PPI used in each therapy (Figure 5).

Regarding the cumulative eradication rate, the “Japanese eradication strategy” provided a consistent annual eradication rate without a decrease over time. Overall, 1499 (76.0%) patients were relieved of *H. pylori* by this strategy. After eliminating from consideration patients lost to follow up, 1872 patients had their *H. pylori* status judged after the first-line treatment and 235 after second-line treatment. Success in eradication was achieved in 1289 patients after first-line treatment and in an additional 210 patients after second-line treatment. Failure was finally noted in 25 patients. In summary, the eradication rate by PP was 68.9% for first-line treatment, 89.4% for second-line treatment and 98.4% for both therapies combined.



## Discussions

Recent studies suggest that eradication rates achieved by treatment such as first-line therapy in Japan that includes clarithromycin have decreased to 70%-85% because of the increasing resistance to clarithromycin (2). Gisbert et al. reported no evidence of a tendency of the eradication rate to decrease through use of standard triple therapy during the 12 years from 1998 to 2010 in a Spanish hospital; the overall eradication rate was 83.4% for ITT and 84.5% for PP analyses (5). They calculated that the mean resistance rate was 8% based on 13 Spanish studies (3293 patients) that evaluated clarithromycin resistance (6) and described recent studies that showed clarithromycin resistance rate of 12% in Spain in 2008 and 2009 (5). Although the use of antibiotics brought about development of primary resistance to clarithromycin in *H. pylori*, it was widely used for respiratory diseases (7). Horiki et al. investigated data on 3521 patients in a hospital in Tokyo, Japan from 1996 to 2008 and showed that clarithromycin resistance had increased to approximately 30% until 2004, and thereafter remained at that high rate (8). Kobayashi et al reported that clarithromycin resistance in Japan had increased yearly from 18.9% to 27.7% in the period from 2002 to 2005 through examination of 3,707 *H. pylori* isolates collected from patients from 36 medical facilities representing different geographical regions of Japan (9). Recent study in

Nagoya, Japan reported that the eradication rate by triple therapy based on PPI, amoxicillin, and clarithromycin declined over time from 90.6% (1997-2000) to 80.2% (2001-2003), 76.0% (2004-2006), and 74.8% (2007-2008), and that clarithromycin resistance rose from 8.7% (1997-2000) to 23.5% (2001-2003), 26.7% (2004-2006), and 34.5% (2007-2008) (3). In our study, the annual eradication rate by the use of first-line therapy that included clarithromycin decreased from 2000 to 2009, similarly to those rates shown in those above-described studies (figure 2). But, our eradication rates about first line therapy seemed to be relatively low compared to their data. We extracted the subject who had 100% drug adherence to exclude the influence of drug adherence. As a result, the eradication rate was 70.0% for first-line treatment. Unfortunately we didn't check drug resistance about our patients, It might be some difference about clarithromycin resistance rate in our population and theirs.

On the other hand, our data showed that the annual eradication rate for second-line therapy was maintained. A multicenter prospective study in Japan reported that the eradication rate by triple therapy based on rabeprazole, amoxicillin, and metronidazole was 92.8% (4). Our data was a match for that. An antimicrobial susceptibility test for *H. pylori* before second-line therapy is often performed but because of the invasiveness of a biopsy, cost, and low rate of metronidazole resistance (9), a drug susceptibility test is

not necessarily required before second-line therapy in Japan (10). In addition, metronidazole in vitro resistance does not reflect that in vivo (11). Murakami et al. reported that metronidazole resistance reduced the eradication rate by approximately 40% (12), but noted that only 14 subjects were studied. They also reported an eradication rate for metronidazole-resistant strains of 82%, that is, 18 successes among 22 patients, by treatment that included rabeprazole 20 mg b. d. (13). These findings indicated that empirically a second-line PPI/AM regimen was very effective in Japan. The total first-line eradication rate from 2000 to 2009 was 65.3% for ITT and 68.9% for PP analyses. Graham et al. graded an eradication rate below 80% as “F,” which meant “unacceptable” (14). According to that criterion, our result was scored “F”. Then, from the viewpoint of successive therapies, the Japanese cumulative eradication rate of 76.0% ITT may appear poor. That this cumulative eradication rate was low was because 333 patients who did not have second-line therapy and were considered lost to follow up were among the 583 failures judged after first-line therapy. Rokkas et al. reported that cumulative eradication rates that included results of first- and second-line regimens proposed by the Maastricht III consensus and a third-line empirical regimen with levofloxacin were 89.6% ITT and 98.1% PP (15). If all of those Japanese patients judged as failures after first-line therapy had second-line therapy, eradication would

have been ultimately judged as successful in almost all. In fact, the “Japanese eradication strategy” provided a 98.4% PP cumulative eradication rate, which was good compared with the European strategy. It is often said that a PPI/AM regimen should be the first-line therapy. We reported that quadruple therapy, which added metronidazole to the PPI/AC regimen, provided a much better cure rate than PPI/AC regimen (16)(17). But we would not use metronidazole as a first-line treatment because this therapy was approved without a clinical trial in Japan (1), overuse will cause an increase in bacterial resistance, and it has been noted that metronidazole had carcinogenic potential in humans (18).

The most prescribed PPI in our subjects was lansoprazole. With regard to the kinds of PPI included in eradication therapy, lansoprazole was prescribed from 2000, omeprazole from 2002 and rabeprazole from 2007, and each of these drugs was covered by the national health insurance system in Japan (figure 4). We previously reported that the kind of PPI was not associated with a significant difference in the cure rate in 221 patients with peptic ulcer disease (19). Our current data similarly indicated no significant differences among the three PPIs in patients throughout the 10-year period (figure 5), and the same results were shown in the three years from 2007 when rabeprazole became available. PPIs are metabolized by several cytochrome P450

enzymes, and a mutation in CYP2C19 adversely effects the metabolism of PPIs. This metabolism has some difference in three PPIs for the ratio of the cytochrome P450 enzymes. CYP2C19 genotype is one reason for eradication failure because that weakened the efficacy of PPI, especially omeprazole and lansoprazole more than rabeprazole, among extensive metabolizer (20). We didn't check CYP2C19 about our patients, but in Japan, approximately 19-23% of individuals are poor metabolizers, which is a larger number compared with those in other countries (21). It might be one reason for the lack of a significant difference among the three PPIs.

With regard to treatment success, it is said that a major factor was not only drug susceptibility but compliance (22). In Japan, a combination treatment is provided as Lansap<sup>®</sup>, which consists of lansoprazole, amoxicillin, and clarithromycin in one package, and Lanpion<sup>®</sup>, which consists of lansoprazole , amoxicillin, and metronidazole in one package (23). These are convenient for doctors and patients; therefore, this is one reason for the frequent use of lansoprazole. However, no significant change in eradication rate was found in comparison with therapies that included omeprazole or rabeprazole. In conclusion, although the eradication rate for first-line PPI/AC treatment has been decreasing, the “Japanese eradication strategy” of PPI/AC to PPI/AM provides an acceptable eradication rate. Even though the use of

PPI/AC alone did not provide complete eradication success, a first-line strategy that considers not only the eradication rate, but the safety, usefulness, and low cost associated with PPI/AC should be given careful consideration.

## **Acknowledgements and disclosures**

Competing interests: the authors have no competing interest.

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**Table 1.** Patient characteristics, background disease, prescribed PPI, and results of the treatment

	First-line therapy	Second-line therapy
Age (y)	55.8±10.5	55.0±11.2
Gender (M/F)	1162 / 811	125/125
Background disease		
Gastric ulcer	396	38
Duodenal ulcer	447	51
Gastroduodenal ulcer	177	15
Gastritis	699	114
Other	254	32
Prescribed PPI		
Lansoprazole	1603	134
Omeprazole	54	25
Rabeprazole	316	91
Treatment success	1289	210
Treatment failure	583	25
Lost to follow up	101	15

## Figure legends

Figure 1. Patients were diagnosed as having *H. pylori* infection and received first-line PPI/AC therapy. After the first therapy, some of the failure cases were administered PPI/AM therapy. Patients who did not receive evaluation of success were considered lost to follow up.

\* PPI/AC, proton pump inhibitor, amoxicillin and clarithromycin.

\* \* PPI/AM, proton pump inhibitor, amoxicillin and metronidazole.

Figure 2. Annual eradication rate for each therapy.

Cumulative rate was with success of second-line therapy added to that of first-line therapy. Statistical analysis was evaluated by the Cochran-Armitage trend test. Eradication rate of first-line therapy gradually but significantly decreased in 10 years ( $p=0.0243$ ). Second-line and cumulative eradication rates indicated no change in annual eradication rate ( $p=0.715, 0.239$ ).

Figure 3. Kinds of PPIs prescribed.

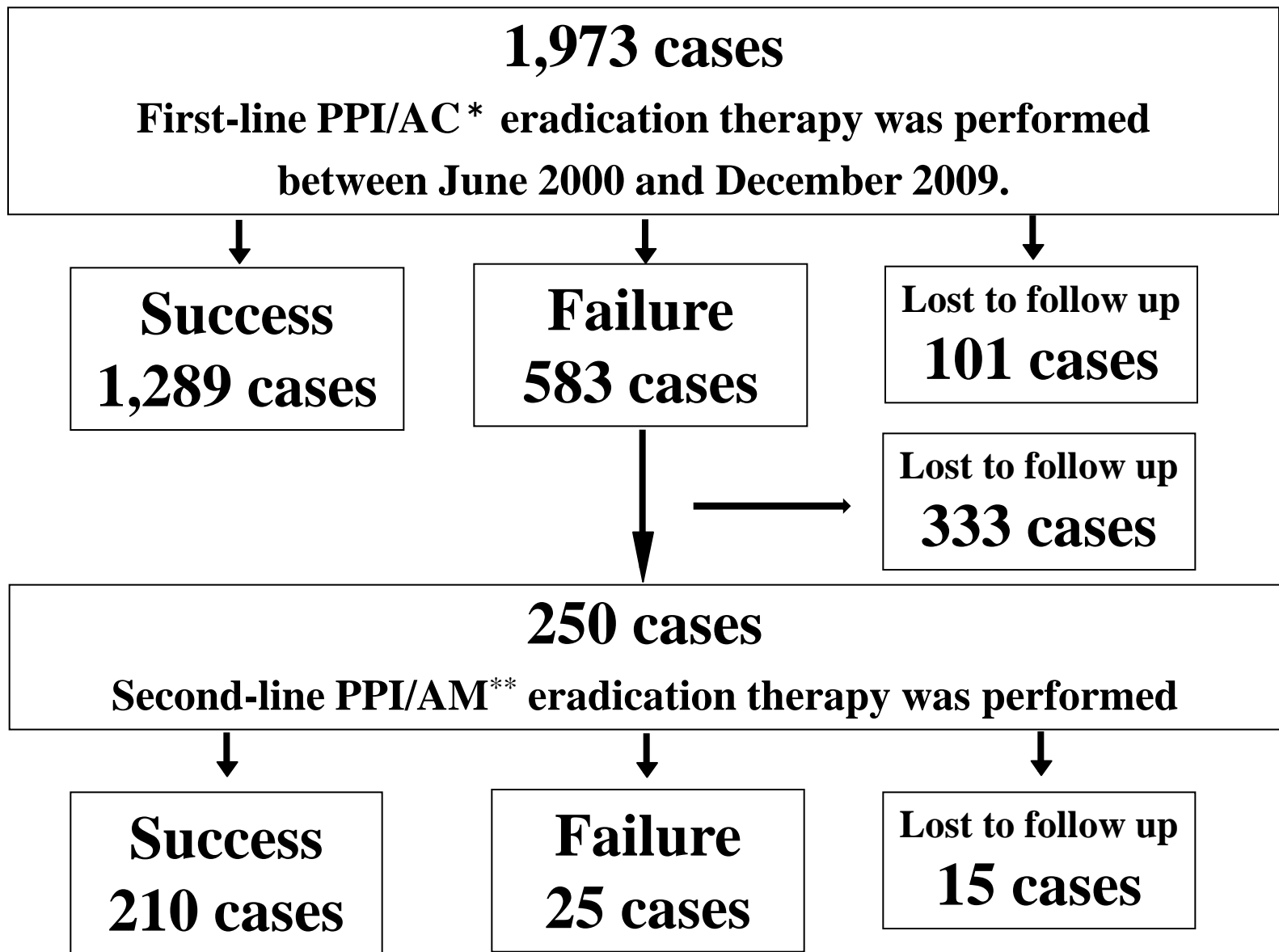
Most prescribed PPI in both first-line and second-line therapy was lansoprazole (first: 81.2%, second: 53.6%).

Figure 4. Annual prescription in each PPI

Most prescribed PPI through the first line therapy and second one was lansoprazole. Prescription of rabeprazole had increased from 2007, from which rabeprazole was covered by the national health insurance system in Japan.

Figure 5. Eradication rate for each PPI.

Eradication rate did not differ according to the kind of PPI for each therapy.

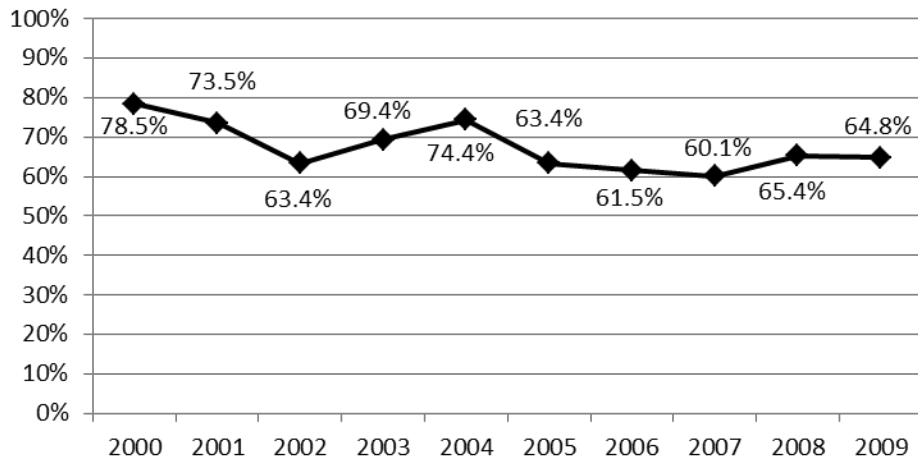


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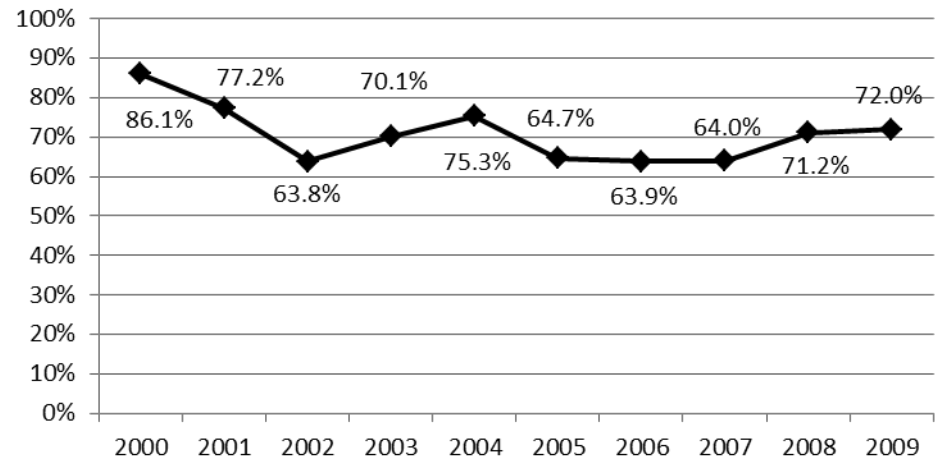
\* PPI/AC, proton pump inhibitor, amoxicillin and clarithromycin.

\*\* PPI/AM, proton pump inhibitor, amoxicillin and metronidazole.

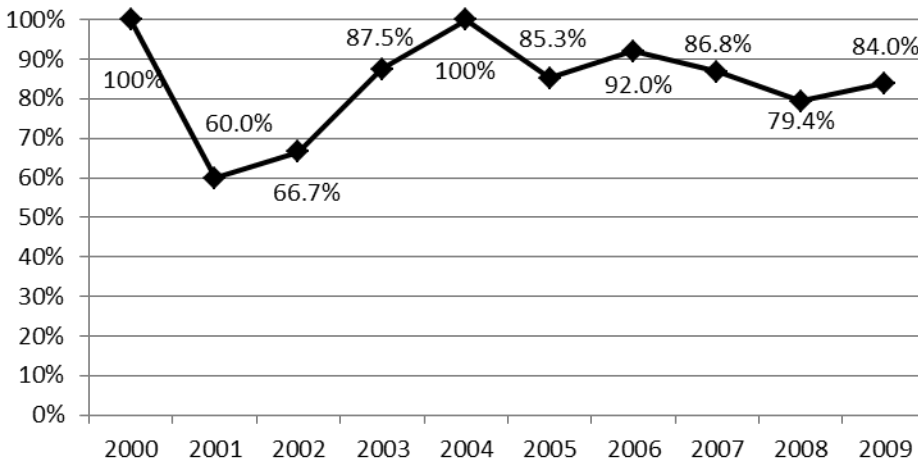
**(a) First line eradication rates (ITT)**



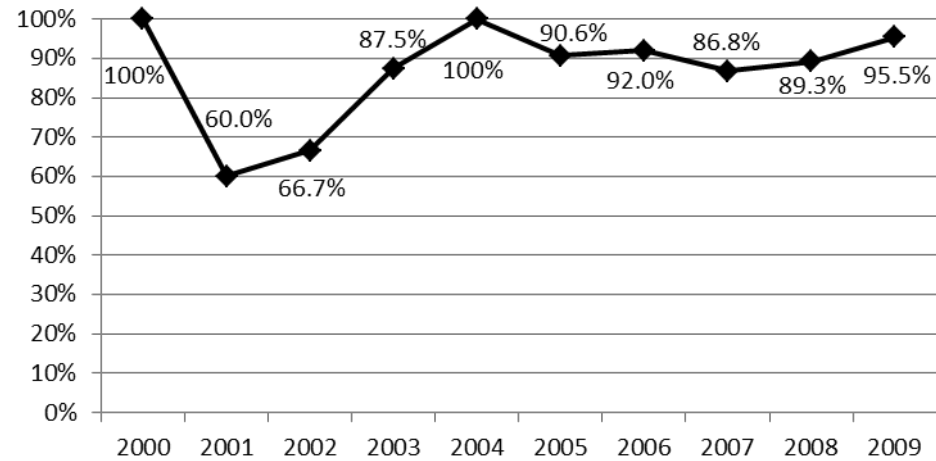
**(b) First line eradication rates (PP)**



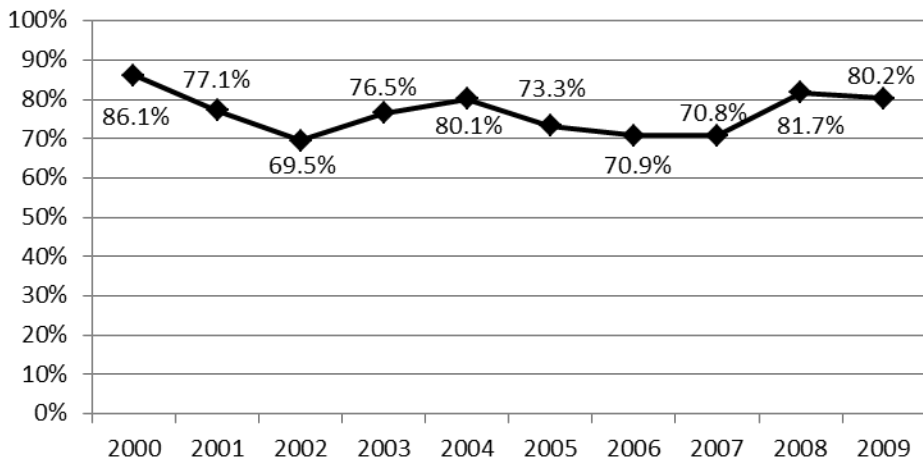
**(c) Second line eradication rates (ITT)**



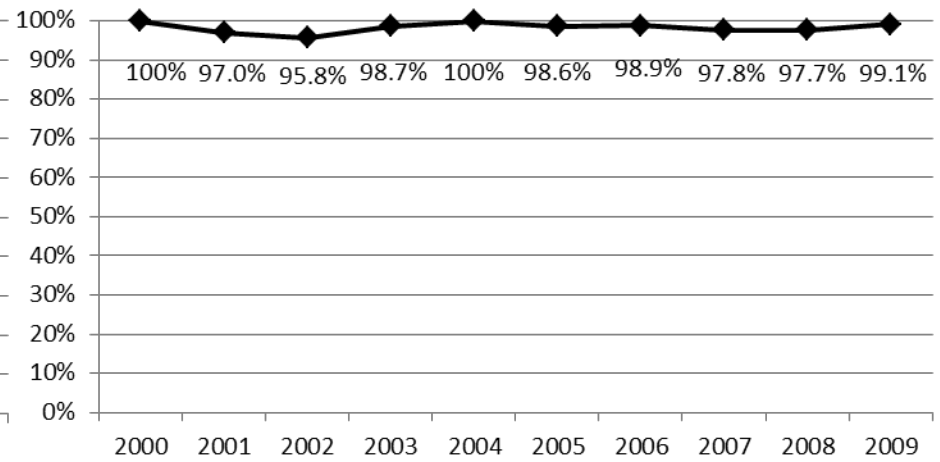
**(d) second line eradication rates (PP)**



**(e) Cumulative eradication rates (ITT)**

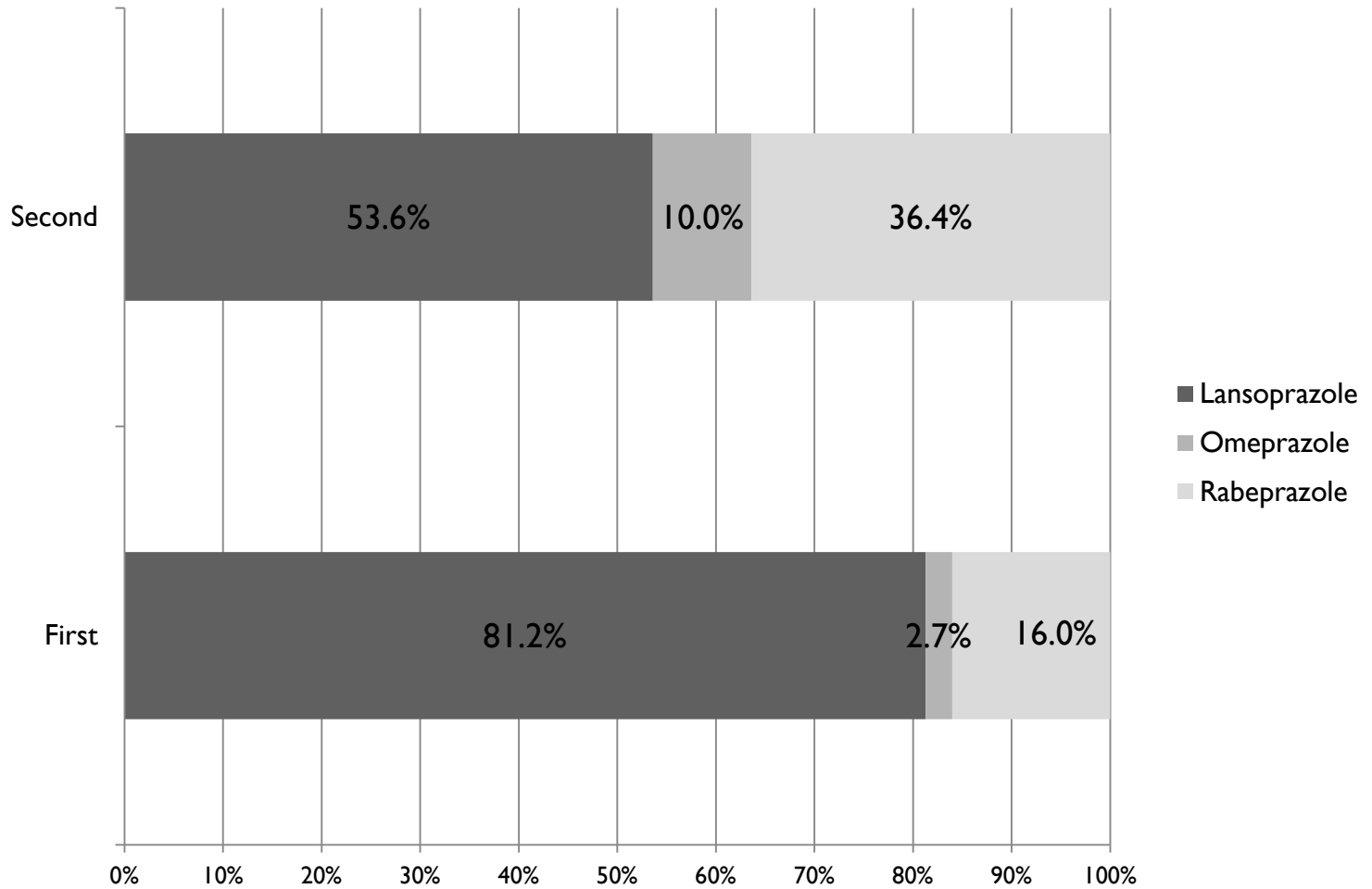


**(f) Cumulative eradication rates (PP)**



**Figure 2.** Annual eradication rate for each therapy.

Cumulative rate was with success of second-line therapy added to that of first-line therapy. Statistical analysis was evaluated by the Cochran-Armitage trend test. Eradication rate of first-line therapy gradually but significantly decreased in 10 years ( $p=0.0243$ ). Second-line and cumulative eradication rates indicated no change in annual eradication rate ( $p=0.715, 0.239$ ).

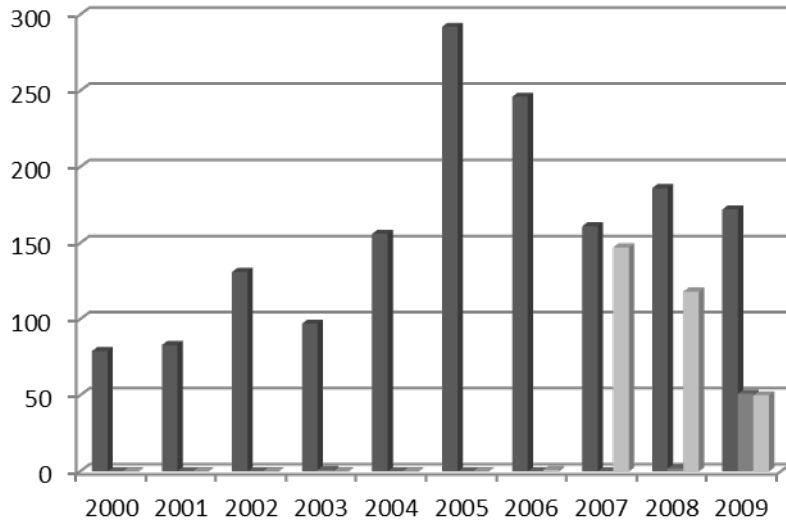


**Figure 3.** Kinds of PPIs prescribed.

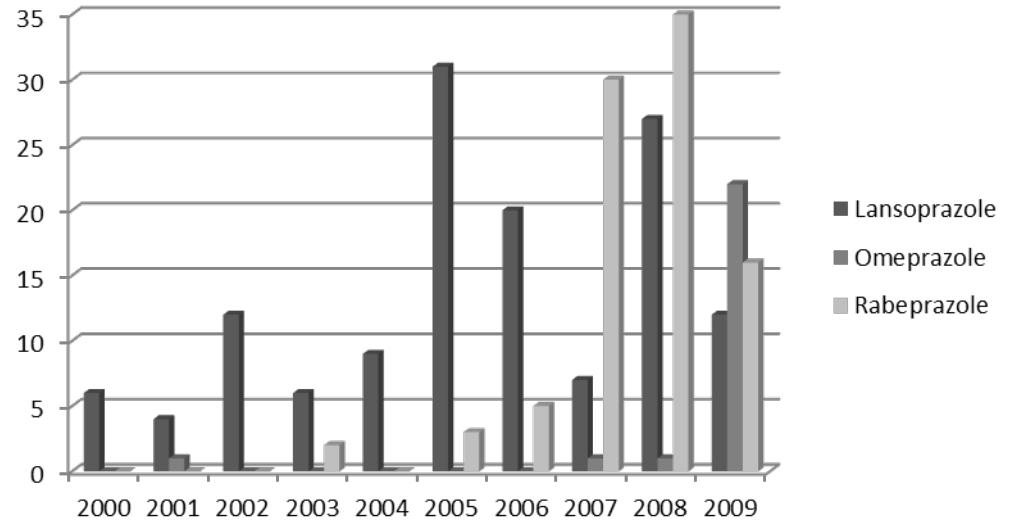
Most prescribed PPI in both first-line and second-line therapy was lansoprazole (first: 81.2%, second: 53.6%).



(a) First line therapy

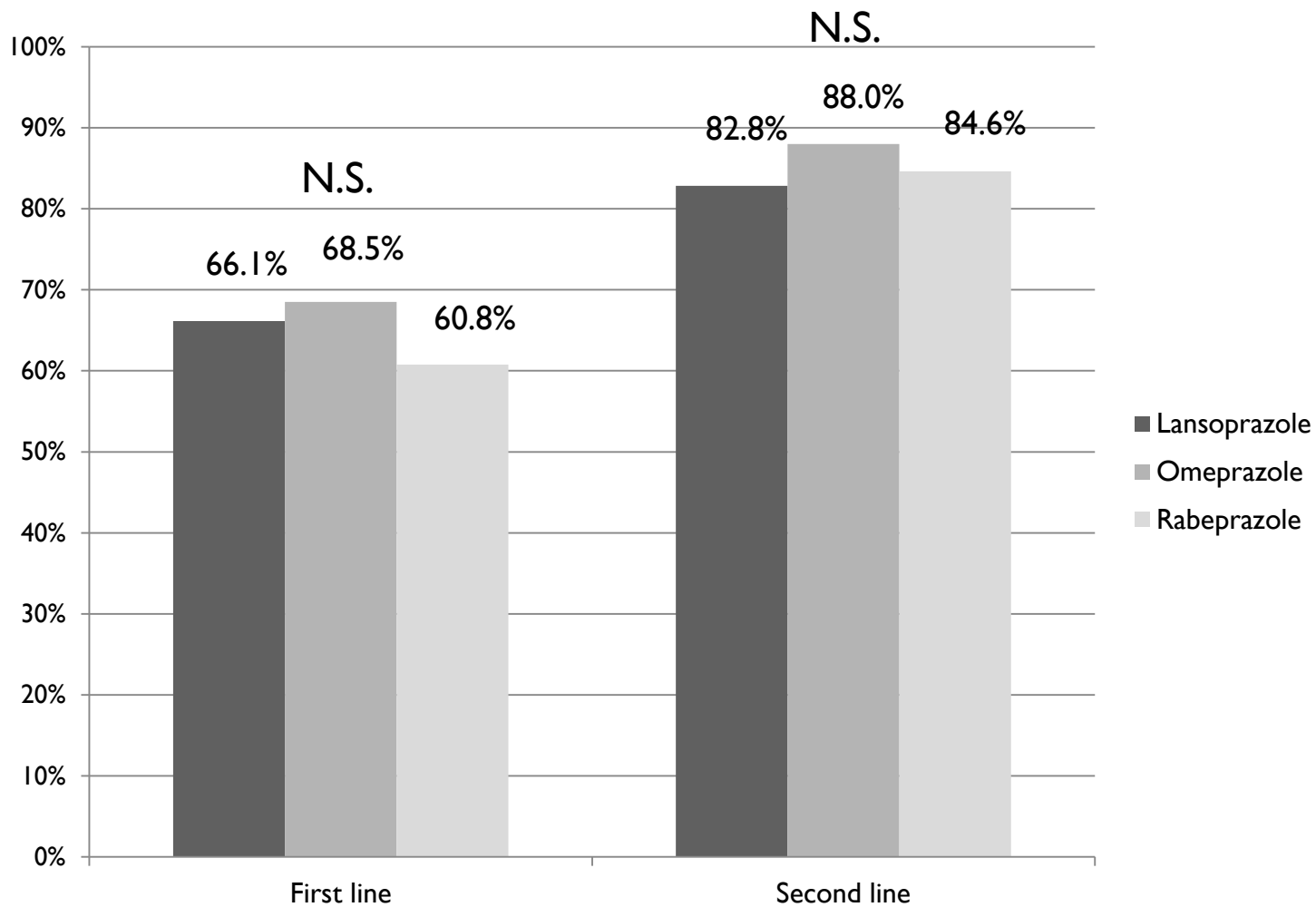


(b) Second line therapy



**Figure 4.** Annual prescription in each PPI

Most prescribed PPI through the first line therapy and second one was lansoprazole. Prescription of rabeprazole had increased from 2007, from which rabeprazole was covered by the national health insurance system in Japan.



**Figure 5.** Eradication rate for each PPI.  
 Eradication rate did not differ according to the kind of PPI for each therapy.