

ORIGINAL ARTICLE

The effect of the use of proton pump inhibitors, serotonin uptake inhibitors, antihypertensive, and anti-inflammatory drugs on clinical outcomes of functional dental implants: A retrospective study

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Abstract

Objective: The present retrospective study investigated the effect of chronic intake of proton pump inhibitors, selective serotonin uptake inhibitors, anti-inflammatory, and antihypertensive drugs on the survival of dental implants and on the occurrence of peri-implantitis.

Materials and methods: Survival analyses for implant failure and peri-implantitis were performed patient level for each drug subcategory and for risk factors. The HR for each drug was calculated with adjusted models as compared with a control group made of subjects not assuming the specific drug. Multilevel logistic regression was used to explore the influence of implant-level and patient-level variables on the outcomes.

Results: A total of 270 subjects receiving 1118 dental implants were included, with a mean follow-up time of 5.19 ± 4.22 years. After 10 years, the survival rate was 86.9% (patient level), and according to survival analysis, 61.3% of subjects were free from peri-implantitis. The use of anti-inflammatory medicines produced a significant effect ($p = .04$) on peri-implantitis as compared to subjects not using the drug, with a 2.7-year drop in the mean survival time. The HR was slightly above the level of significance in a semiaadjusted model ($p = .058$). The multilevel analysis found a significant effect on the entire sample and not when considering only subjects with implants with more than 1-year follow-up.

Conclusions: We found a possible relationship between anti-inflammatory drug use and the occurrence of peri-implantitis in the examined cohort of patients, and no correlation for the other drugs.

KEYWORDS

antihypertensive agents, anti-inflammatory agents, bone resorption, dental implants, peri-implantitis, proton pump inhibitors, serotonin uptake inhibitors

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1 | INTRODUCTION

Dental prosthesis supported by dental implants represents a safe and viable treatment option for full and partial edentulism, whose efficacy over time was demonstrated by several medium- to long-term longitudinal studies performed on representative samples (Corbella et al., 2021; Francetti et al., 2019; French et al., 2021; Howe et al., 2019).

One recently published study on the trend of the use of dental implants in the United States reported a substantial increase in dental implants to use between 1999 and 2016, and the trend of such increase is predicted to maintain for the next years (Elani et al., 2018). Moreover, the increment in the prevalence of dental implants was more evident (12.9%) among people 65 to 74 years old, more in highly educated individuals than less educated ones, with equal distribution among males and females (Elani et al., 2018). In Europe, the results of a questionnaire administered to a pool of experts in implant dentistry confirmed the predicted increase in implant treatment demands in the population, due to the growth of elder population and, consequently, of the number of subjects with partial or full edentulism (Sanz et al., 2019). In the context of an increase in treatments also peri-implant complications are expected to increase, consequently (Sanz et al., 2019).

The current and predicted trends of global demography and of dental implants treated potentially imply the increase in treatment needs in subjects assuming medicines and exposed to a number of systemic diseases that may have an impact on implant therapy (Donos & Calciolari, 2014; Mombelli & Cionca, 2006). Indeed, it is known that the intake of medicines such as diuretics, beta-blockers, and antihypertensive drugs in general, anti-inflammatories, and others may have an effect on modulating the bone metabolism (Vestergaard, 2008). Other drugs, belonging to the group of proton pump inhibitors (PPIs), might have a known effect on bone physiology (Briganti et al., 2021), and were described in one study to determine higher peri-implant bone resorption over time under prosthetic loading (Aghaloo et al., 2019; Ducommun et al., 2019; Ursomanno et al., 2020).

The use of some drugs is very frequent in the general population that underwent implant surgery. In Italy, the annual report of the Italian Medicines Agency (AIFA) has presented a list of the 30 active principles with the highest spending rate in the country (Centre, 2020): among them, we can find four PPIs (pan-toprazole is the second in the list), antihypertensive drugs, many anti-inflammatory principles and selective serotonin reuptake inhibitors (SSRI) (escitalopram). Central nervous system drugs, including SSRIs with the highest consumption (28.4 defined daily doses [DDD], +1.5% in the last year), represent the sixth most expensive therapeutic category with a higher prevalence of use in women starting from the age of 35, consistently with gender differences in the frequency of neuropsychiatric diseases. In particular, sertraline was found to be among the top 30 medications with the greatest variation in cost.

One report published in 2020 about the use of medicines among older people (more than 65 years old) in four European countries (England, Poland, Portugal, Slovakia), has shown that PPIs (different active principles) were amongst the ten most prescribed drugs together with antihypertensive and anti-inflammatory medicines (Strampelli et al., 2020). In a study conducted on the Icelandic population, Hálfðánarson et al. analyzed the consumption trends of PPIs between 2003 and 2015, highlighting an increase in the prevalence of this class of drugs (from 8.5 to 15.5 per 100 people per year) combined with the increase in dosages and duration of therapy (Halfdanarson et al., 2018).

Finally, it is interesting to note how the recent events related to the Covid-19 pandemic have influenced the pharmaceutical market: this is visible for example in the record increase in Spain regarding the intake of drugs for the central nervous system (+7%) or the over-prescription of mental health and anxiety medications in the United States (6 million and 2 million more, respectively) (Ayati et al., 2020).

The aim of the present retrospective study was to investigate the effect of the intake of four very common drugs (PPIs, SSRIs, antihypertensive principles, anti-inflammatory substances) on the occurrence of peri-implantitis and dental implant failure in a cohort of subjects.

2 | MATERIALS AND METHODS

2.1 | Study design, setting, and authorization

The present is a retrospective study whose protocol was approved by the Ethical Committee of the IRCCS Ospedale San Raffaele in Milan, Italy (31/INT/2021), which recommended the use of anonymized data as prescribed. All the phases of the study were carried on according to the principles embodied in the Helsinki Declaration for Research on Human Subjects (World Medical Association, 2013). For reporting the study, the authors followed the instructions included in the "Strengthening the Reporting of Observational studies in Epidemiology (STROBE)" guidelines for observational studies (von Elm et al., 2014).

2.2 | Participants

For the aims of the study the clinical and radiographic records of all patients treated with implant-supported prosthetic rehabilitation in the Dental Clinic of the IRCCS Istituto Ortopedico Galeazzi, in Milan, Italy in the period ranging from 1st January 2004 and 1st January 2021 were screened for inclusion on the basis of the following criteria: (i) the records must be referred to subjects who were 18 years old or older at the time of implant placement and who provided their written informed consent for the treatment and for using the radiographic and clinical data for the research purposes; (ii) the record must be referred to subjects treated with any type of implant-supported restoration (single tooth,

fixed-partial prosthesis (FPDs), full-arch implant-supported rehabilitations (FAISRs).

Records not providing enough information about the prosthetic restoration and about the use or not of the drugs that are the object of the present investigation were excluded.

2.3 | Outcome variables and data measurement

The main outcomes considered in the study were cumulative implant survival (patient level) and the occurrence of peri-implantitis in subjects who continuously used one of the four drug categories considered (during the entire period of observation if less than 5 years or for at least 5 years during the observation period) as compared to the group of subjects not assuming the drug. The drugs category considered were: (i) PPI (ATC code A02BC); (ii) SSRI (ATC code N06AB); (iii) anti-inflammatory drugs (ATC codes: M01, H02) (cortisone, acetylsalicylic acid [ASA], or others); (iv) antihypertensive drugs (ATC code: C02) (Angiotensin-converting enzyme [ACE] inhibitors, Beta-blockers, diuretics, Ca-antagonists, Angiotensin II receptor antagonists, or others). The intake of one drug was assessed by a questionnaire administered to the subjects.

The following definitions were adopted in the study, on the basis of previously published papers (Corbella et al., 2021; Francetti et al., 2019): (i) *implant survival* was defined on the basis of the presence of the dental implant in situ, supporting a functional dental prosthesis; (ii) *implant failure* identified one dental implant that was lost spontaneously or removed due to failure of osseointegration; (iii) *peri-implantitis* was defined on the basis of the criteria proposed by Berglundh et al. (2018), which were the presence of signs of inflammation (bleeding and/or suppuration after probing), radiographic bone loss beyond crestal bone resorption due to initial remodeling or, if the one year radiograph is missing, presence of bone level positioned ≥ 3 mm apical to the most coronal portion of the intraosseous portion of the implant body, and presence of increased probing depth as compared to previous measurements, if available.

The periapical radiographs used for the investigation were taken with paralleling technique using phosphor plate digital images with an exposure ranging from 0.16 to 0.22s. The quality of the radiographs was appraised by adopting the criteria for dental radiography of the Faculty of General Dental Practice (UK). Two operators (SC, BM), previously calibrated, independently evaluated the radiographs for assessing, in duplicate, the presence of bone resorption. In case of disagreement (7% of the total cases) in the evaluation, a third operator was involved (LF) and the disagreement was resolved by discussion. The measurements on radiographs were taken by using the software ImageJ (Rasband, W.S., ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, <https://imagej.nih.gov/ij/>, 1997–2016).

The history of periodontitis status was assessed before the first implant placement and the periodontal status was evaluated during each follow-up visit. One subject was defined as having a

history of periodontitis following the criteria published in 2018, namely if the subjects are affected by interdental CAL ≥ 2 nonadjacent teeth, or buccal/oral CAL ≥ 3 mm with PPD > 3 mm is detectable at ≥ 2 teeth (Tonetti et al., 2018), and it was evaluated on the basis of clinical and radiographic records. The smoking status was assessed at the time of the first implant placement, by asking the patient.

In case of multiple implants with peri-implantitis, we considered the one with the shortest follow-up as the first occurrence of the disease.

2.4 | Quantitative analysis and statistical methods

The statistical analysis was carried out using dedicated software (SPSS, version 22, IBM).

The normality of the distributions was assessed by Shapiro–Wilk and Kolmogorov–Smirnov tests. For descriptive statistics we calculated mean value, median value, range, and standard deviation for each continuously distributed variable, whilst, for categorical variables, we calculated frequencies.

The analysis of survival (considering implant failure and occurrence of peri-implantitis as events) was performed by using Kaplan–Meier estimate, using the time of the last visit or the time of event occurrence as censoring time. The tests log-rank, Tarone–Ware, and Breslow were used to evaluate the differences between subjects assuming or not a specific drug category, as specified before. The ancillary analysis compared the survival curves for subjects with or without a history of periodontitis and with or without smoking habit.

The measure of the effect (hazard ratio [HR]) of assuming one specific drug category on the survival curves was calculated by means of Cox regression analysis, adopting three different models: one adjusted for number of implants per patient (Model A), one adjusted for number of implants and periodontal status (presence or absence of history of periodontitis) (Model B), one adjusted for number of implants, periodontal and smoking status (Model C).

Multilevel logistic regression analysis was also performed. The patient was considered as a random effect whilst prosthesis type, fixation, loading time, drug use, smoking, and periodontal status, follow-up, and quadratic follow-up were considered as fixed effects.

All the analyses were performed on the entire sample and separately, considering only subjects with more than 1-year follow-up.

For all analyses, the level of significance was posed at $p < .05$.

3 | RESULTS

3.1 | Participants

The preliminary selection of clinical records retrieved 288 items; 18 subjects were excluded because of incomplete clinical documentation (16 for missing information about drug intake, two for missing information about characteristics of the implant restoration).

3.2 | Descriptive data

Finally, the study included a total of 270 subjects who received 1118 dental implants with moderately rough surface. Two-hundred forty-two subjects have a follow-up of more than 1 year from loading. The characteristics of the sample are presented in [Table 1](#).

The mean follow-up time was 5.19 ± 4.22 years (median 4.04 years [0.4–16.2 years]) for the entire sample and it was 5.81 ± 4.02 years (median 4.91 years [1.01–16.2 years]) considering only subjects with more than 1-year follow-up.

3.3 | Main results

Considering the entire sample, regarding the occurrence of implant failure, the 10 years survival rate (patient level) was 86.9% (93.8% implant level), having a mean survival time of 14.2 ± 0.4 years (median not available) ([Figure 1](#)); regarding the occurrence of peri-implantitis, the 10 years survival rate (patient level) was 61.3% (73.1% implant level), having a mean survival time of 11.4 ± 0.5 years (median 11.4 years [10.3–12.6 years]). The prevalence of peri-implantitis was 18.5% (50 subjects with peri-implantitis out of 270). Of the 270 subjects examined, the diagnosis of peri-implant health/peri-implantitis was done without baseline radiological documentation in 18 cases, 6.7% of the entire sample (26 implants).

Regarding the comparison between the survival curves of subjects assuming or not one of the drugs under examination, we found that the survival curves were not significantly different for what concerns implant failure ($p > .05$). Conversely, a significant difference ($p = .04$) was found between subjects taking anti-inflammatory drugs and subjects not taking the medicine, for what concerns the occurrence of peri-implantitis ([Figure 2](#)). Indeed, the use of anti-inflammatory drugs reduced the median survival time to 2.8 years (being 12.0 years [10.7–13.4 years] for people not assuming the drug and 9.2 years [7.1–11.4 years] for people assuming them). The associations of two or more drug categories did not produce any statistically significant effect on survival curves ($p > .05$). The results of regression analysis for the entire sample were shown in [Table 2](#). In the three models, the effect of the use of anti-inflammatory drugs on the occurrence of peri-implantitis decreased to not significant values but resulted to be near statistical significance after adjustment for periodontal status ($p = .058$).

When examining the subsample of subjects with more than 1-year follow-up no effect of drug use was found on implant survival. The use of anti-inflammatory drugs influenced the survival curves referred to as peri-implantitis ([Figure 3](#)) ($p = .04$). The results of the regression analysis (shown in [Table 3](#)) for the subsample did not show any significant effect.

The survival curve (for the occurrence of peri-implantitis) was significantly different between smokers and nonsmokers, being a mean survival time of 9.1 years [8.8–9.5 years] for nonsmokers and 7.6 years [6.7–8.6 years] for smokers. For periodontitis, no differences were found considering the entire sample, but curves differ

significantly when considering subjects with more than 3.5 years of follow-up. No differences were found for both smoking and periodontal status regarding implant failure.

The results of the multilevel analysis were presented in [Appendix S2](#). The analysis revealed that the use of anti-inflammatory drugs has a negative significant effect on the occurrence of peri-implantitis in the entire sample (OR = 2.123, 95% CI: 1.018–7.560, $p = .042$), while the effect is not significant when considering the subgroup of subjects with more than 1-year follow-up ($p = .065$).

4 | DISCUSSION

The present paper reported the results of an observational investigation on a cohort of subjects treated in a University Clinic. The evaluation of survival curves revealed that the use of anti-inflammatory drugs had a statistically significant effect in lowering the mean time free from peri-implantitis (patient level).

The results of our study were partially in contradiction with the ones presented in scientific literature.

Two retrospective studies on a significant number of implants reported a detrimental effect on implant survival of the assumption of PPIs: Chrcanovic et al. (Chrcanovic et al., 2017a) found that the assumption of PPIs can more than double the risk of incurring in implant failure and similar results were found by Wu (Wu et al., 2017) in a study with a short follow-up. Partially, the explanation of the differences found could be ascribed to the different analyses of the data: in our investigation we performed a patient-level analysis, which is more accurate, in our opinion, to assess the effects of systemically prescribed drugs on implant failure. Indeed, the study by Altay and coworkers published in 2019, found that the correlation between PPI assumption and implant failure was significant at the implant level but not significant at the patient level (Altay et al., 2019), partially confirming our assumption. Another recently published study on a cohort of 99 patients (458 implants) found a significant protective effect of the use of PPIs and anticoagulant active substances towards the development of peri-implantitis and this effect was explained based on their anti-inflammatory effect (Romandini et al., 2021). Thus, the effect of PPIs on peri-implant tissues is still controversial.

With particular regard to the assumption of SSRIs, one systematic review of the literature on two studies (Chrcanovic et al., 2017b; Wu et al., 2014) found a significant effect in increasing the possibility of implant failure (Chappuis et al., 2018). Other studies not included in the meta-analysis addressed the same topic. One study published in 2018 on a cohort composed of 631 patients (36 using SSRIs) with a total of 2055 implants failed to find a significant correlation between SSRIs assumption and implant failure, without any analysis of the correlation between SSRIs and peri-implantitis (Altay et al., 2018). Another paper published in 2018 explored the effect of SSRIs on 352 patients with 680 dental implants (Deepa et al., 2018). The authors found a certain difference between assumers and not assumers in terms of implant failure, even though the effect of important

TABLE 1 Characteristics of the sample. Active principles are showed in Appendix S2

Subjects' demographics	All subjects	≥1 year from loading
Females; males	154 (57.0%); 116 (43.0%)	143 (59.0%); 99 (41.0%)
Age at surgery (years)	58.5 ± 12.2 (median 60.4; range 20.8–85.7)	58.6 ± 12.0 (median 61.2; range 20.8–85.7)
History of periodontitis	153 (56.7%)	148 (61.1%)
Current smokers	62 (23.0%)	61 (25.2%)
Nonsmokers	208 (77.0%)	181 (74.8%)
Former smokers	29 (10.7%)	27 (11.1%)
Medicines assumption	All subjects	>1 year from loading
Proton pump inhibitors (PPIs)	26 (9.6%)	25 (10.3%)
Selective serotonin reuptake inhibitors (SSRIs)	24 (8.9%)	21 (8.7%)
Anti-inflammatory drugs	31 (11.5%)	30 (12.4%)
Acetylsalicylic acid (ASA)	23 (8.5%)	22 (9.1%)
Cortisone	3 (1.1%)	3 (1.2%)
Other anti-inflammatory drugs	5 (1.5%)	5 (2.1%)
Antihypertensive drugs	69 (25.6%)	64 (26.4%)
Angiotensin-converting enzyme (ACE) inhibitors	33 (12.2%)	30 (12.4%)
Beta-blockers	23 (8.5%)	21 (8.7%)
Diuretics	20 (7.4%)	19 (7.9%)
Calcium channel blockers	10 (3.7%)	9 (3.7%)
Angiotensin II receptor antagonists	13 (4.8%)	11 (4.5%)
Other antihypertensive drugs	4 (1.5%)	4 (1.7%)
Subjects/Implants	All subjects	>1 year from loading
N° subjects/implants	270/1118	242/988
N° implants per subject	4.14 ± 3.04 (median 4.00; range 1–16)	4.08 ± 3.11 (median 4.00; range 1–16)
Prosthesis type (%)	All subjects	>1 year from loading
Single tooth restoration	36.1% (185 implants)	36.8% (122 implants)
Fixed-partial dentures	21.6% (303 implants)	19.4% (292 implants)
Full-mouth fixed dentures	36.8% (578 implants)	38.8% (540 implants)
Overdentures	5.6% (52 implants)	4.5% (34 implants)
Prosthesis location (%)	All subjects	>1 year from loading
Maxilla	49.9% (556 implants)	49.2% (486 implants)
Mandible	50.1% (562 implants)	50.8% (502 implants)
Prosthesis fixation method (%)	All subjects	>1 year from loading
Cemented	12.7% (145 implants)	13.6% (128 implants)
Screwed	87.3% (973 implants)	86.4% (860 implants)

risk factors was not adequately controlled between the two groups. One recently published retrospective study on 771 patients (1820 implants) examined specifically the effects of antidepressant drugs on dental implant failure (Hakam et al., 2021). Interestingly, since other drug categories, such as serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants, were significantly correlated with implant failure, SSRIs did not demonstrate any significant effect, being the most assumed medicine. Another important issue emerged from the study by Carr and coworkers published in 2019,

that reported that while the history of SSRI assumption was correlated with implant failure, active SSRIs were not significantly associated with an increase of the risk of incurring in implant failure (Carr et al., 2019). The results of the present study did not report any association between SSRIs use and implant failure or peri-implantitis and, in light of the existing literature, such association, although biologically plausible, needs more confirmation.

Our results did not reveal any association also with particular regard to the use of antihypertensive drugs. The literature about the

FIGURE 1 Kaplan–Meier estimate for implant survival considering the entire sample

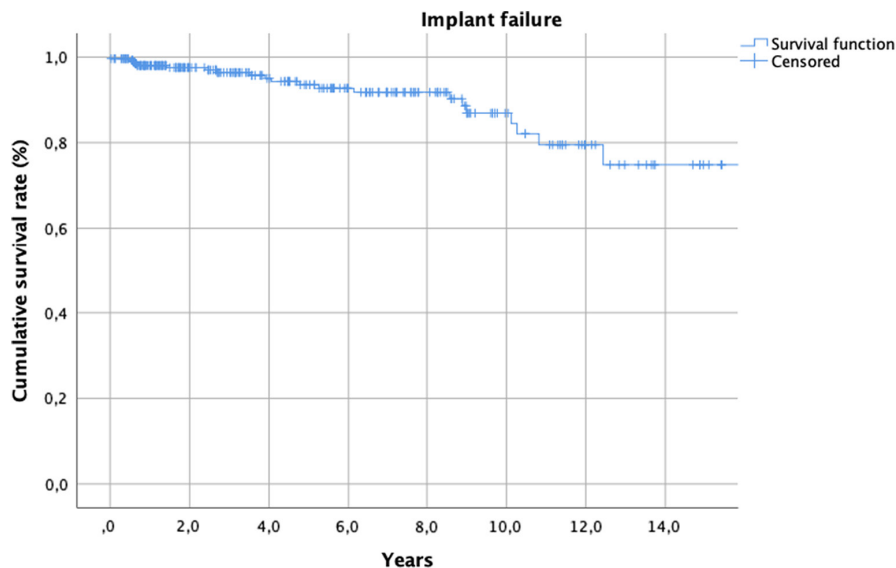
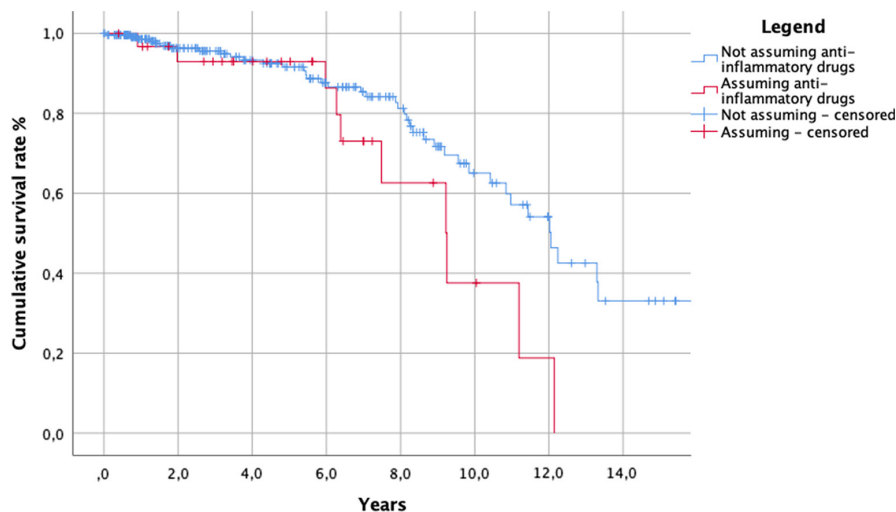


FIGURE 2 Kaplan–Meier estimate comparing people not assuming anti-inflammatory drugs of any type to subjects assuming them for occurrence of peri-implantitis in at least one implant. Entire sample.



topic is, to our knowledge, extremely limited, although the use of such a drug category is widespread worldwide. One paper published by Wu and colleagues in 2016 on 1499 dental implants placed in 728 patients, found a positive effect of the treatment with antihypertensive medicines on implant survival rate over time (Wu et al., 2016).

The effect of the chronic use of anti-inflammatory agents (including ASA) on implant survival was explored in one recent review of the literature (Etikala et al., 2019). Although the authors highlighted that the available studies were extremely heterogeneous, there is biologically plausible evidence that the use of such medications could have a negative effect on implant failure (Winnett et al., 2016). Our results, although not conclusive, showed a detrimental effect of the assumption of NSAIDs in increasing the risk of incurring peri-implantitis, significantly lowering the survival curve for assuming subjects. Such assumption was demonstrated also by multilevel logistic regression analysis, which found a significant effect in the entire cohort and a near-to-significant effect considering only subjects with more than one-year follow-up. It should be noticed that patients assuming anti-inflammatory drugs, especially ASA, may

exhibit an increase in the bleeding indices due to the inhibition of platelet aggregation. This factor should be considered when evaluating the peri-implant tissues, in the context of a diagnostic process including clinical and radiographical parameters.

Even though the present study aimed at studying the effect of assuming common medicines on implant failure and on the occurrence of peri-implantitis, as ancillary analysis, we found a substantial effect of smoking and of history of peri-implantitis, the last particularly significant after 3.5 years from implant placement. Whereas the negative effect of periodontitis on increasing the risk of peri-implantitis is a well-established knowledge (Ferreira et al., 2018; Schwarz et al., 2018), the effect of smoking is plausible but still controversial (Dreyer et al., 2018).

The validity of the results of the study should be weighted considering the limitations of the study design. Firstly, the retrospective nature of the study implied a substantial heterogeneity in the sample for what regards the characteristics of the subjects, the restorations, and the follow-up length; however, the strict inclusion criteria and the fact that the entire cohort was included could have increased

TABLE 2 Regression analysis results (Hazard ratio [CI 95%])

	Implant failure			Peri-implantitis		
	Model A	Model B	Model C	Model A	Model B	Model C
<i>PPI</i>	0.384 [0.046–3.199]	0.431 [0.052–3.597]	0.521 [0.060–4.778]	0.686 [0.257–1.832]	0.710 [0.263–1.918]	0.915 [0.332–2.523]
<i>SSRI</i>	1.959 [0.404–9.511]	2.057 [0.417–10.157]	1.952 [0.395–9.633]	0.715 [0.231–2.213]	0.826 [0.271–2.516]	0.724 [0.235–2.234]
<i>Anti-inflammatory</i>	0.852 [0.192–3.773]	0.954 [0.210–4.329]	0.917 [0.202–4.152]	0.498 [0.241–1.026]	1.959** [0.951–4.033]	1.699 [0.820–3.521]
Acetylsalicylic acid (ASA)	1.102 [0.249–4.871]	1.387 [0.290–6.630]	1.348 [0.282–6.444]	1.838 [0.809–4.175]	1.763 [0.750–4.144]	1.579 [0.667–3.735]
Cortisone	NA	NA	NA	3.020 [0.702–13.000]	3.306 [0.729–15.002]	2.072 [0.432–9.942]
Other anti-inflammatory drugs	NA	NA	NA	NA	NA	NA
<i>Antihypertensive drugs</i>	0.800 [0.255–2.512]	0.935 [0.285–3.071]	0.901 [0.277–2.929]	1.042 [0.528–2.055]	0.997 [0.505–1.967]	0.993 [0.504–1.957]
Angiotensin-converting enzyme (ACE) inhibitors	1.972 [0.245–15.871]	0.611 [0.072–5.161]	0.563 [0.064–4.928]	0.800 [0.318–2.014]	1.350 [0.532–3.428]	1.324 [0.507–3.456]
Beta-blockers	0.334 [0.087–1.287]	3.426 [0.847–13.855]	3.097 [0.759–12.633]	0.625 [0.209–1.871]	1.735 [0.572–5.265]	1.566 [0.504–4.867]
Diuretics	0.853 [0.099–7.336]	1.199 [0.132–10.864]	1.327 [0.143–12.278]	1.131 [0.254–5.038]	0.867 [0.194–3.881]	0.977 [0.217–4.398]
Calcium channel blockers	NA	NA	NA	0.933 [0.119–7.298]	1.028 [0.130–8.146]	1.076 [0.135–8.603]
Angiotensin II receptor antagonists	NA	NA	NA	4.866 [0.619–38.281]	0.200 [0.025–1.583]	0.178 [0.021–1.480]
Other antihypertensive drugs	NA	NA	NA	NA	NA	NA
<i>N° of implants per patient</i>	1.263* [1.133–1.407]	1.244* [1.086–1.426]	1.255* [1.089–1.446]	1.148* [1.046–1.260]	1.135* [1.026–1.255]	1.145* [1.031–1.271]

Abbreviation: NA, not assessed for low number of events.

*Statistically significant $p < .05$; ** $p = .058$.

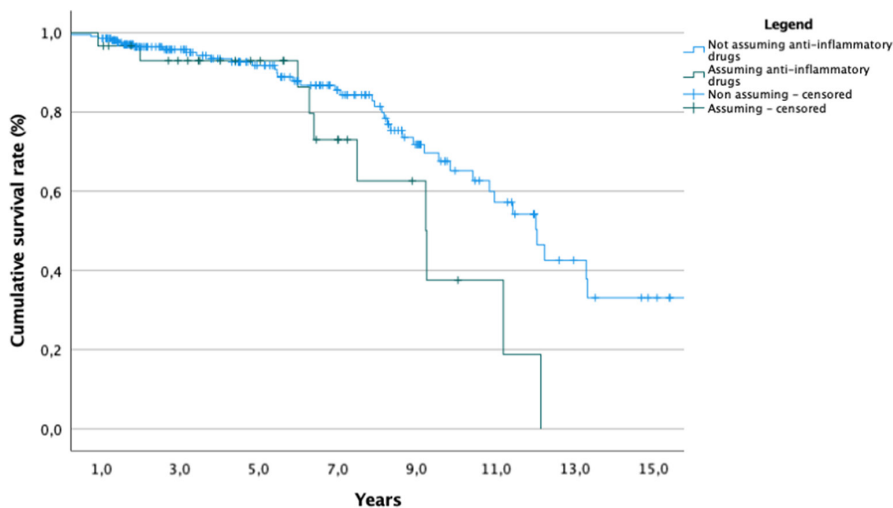


FIGURE 3 Kaplan-Meier estimate comparing people not assuming anti-inflammatory drugs of any type to subjects assuming them for occurrence of peri-implantitis in at least one implant. At least 1-year follow-up.

the representativeness of the sample itself in the context of the entire population. However, we should consider as a limitation the fact that, due to the study design, some subjects may have not returned for follow-up and for maintenance treatment. Moreover, the sample size and, consequently, the loss of statistical power, could be

considered as a factor that could have masked the effect of some drugs on the evaluated outcomes. As an adjunct, the mean follow-up time was relatively short, as compared to other similar studies. Then, the data we analyzed did not provide significant information about the duration, the frequency of assumption, and the dosage of the

TABLE 3 Regression analysis results (Hazard ratio [CI 95%])—At least 1-year follow-up

	Implant failure			Peri-implantitis		
	Model A	Model B	Model C	Model A	Model B	Model C
PPI	0.357 [0.047–2.678]	0.386 [0.051–2.942]	0.441 [0.056–3.438]	0.616 [0.244–1.560]	0.569 [0.223–1.454]	0.684 [0.262–1.785]
SSRI	0.570 [0.076–4.282]	0.656 [0.086–4.989]	0.656 [0.086–4.989]	0.705 [0.250–1.986]	0.695 [0.246–1.961]	0.658 [0.232–1.868]
Anti-inflammatory	0.794 [0.182–3.462]	0.862 [0.198–3.883]	0.668 [0.149–2.982]	2.005* [0.987–4.075]	1.938 [0.950–3.950]	1.653 [0.794–3.443]
Acetylsalicylic acid (ASA)	1.153 [0.266–5.008]	1.200 [0.261–5.517]	0.833 [0.180–3.851]	1.921 [0.856–4.311]	1.760 [0.757–4.088]	1.497 [0.629–3.560]
Cortisone	NA	NA	NA	2.227 [0.529–9.374]	2.781 [0.628–12.321]	1.839 [0.398–8.502]
Other anti-inflammatory drugs	NA	NA	NA	NA	NA	NA
Antihypertensive drugs	0.827 [0.270–2.532]	0.849 [0.274–2.634]	0.795 [0.254–2.487]	1.035 [0.534–2.005]	1.003 [0.516–1.948]	0.963 [0.495–1.873]
Angiotensin-converting enzyme (ACE) inhibitors	0.537 [0.071–4.070]	0.521 [0.069–3.942]	0.599 [0.078–4.590]	1.274 [0.534–3.039]	1.274 [0.534–3.038]	1.135 [0.472–2.730]
Beta-blockers	2.092 [0.592–7.397]	1.866 [0.524–6.650]	1.742 [0.461–6.548]	1.147 [0.404–3.225]	1.094 [0.383–3.125]	0.913 [0.315–2.645]
Diuretics	0.734 [0.098–5.524]	0.841 [0.111–6.400]	0.742 [0.096–5.747]	0.540 [0.131–2.228]	0.525 [0.127–2.167]	0.623 [0.149–2.602]
Calcium channel blockers	NA	NA	NA	1.145 [0.155–8.484]	1.076 [0.145–7.996]	1.210 [0.162–9.041]
Angiotensin II receptor antagonists	NA	NA	NA	0.314 [0.043–2.279]	0.297 [0.041–2.160]	0.270 [0.037–1.973]
Other antihypertensive drugs	NA	NA	NA	NA	NA	NA
N° of implants per patient	0.982 [0.843–1.145]	0.945 [0.802–1.115]	0.948 [0.813–1.105]	0.959 [0.871–1.057]	0.950 [0.860–1.050]	0.972 [0.881–1.074]

Abbreviation: NA, not assessed for low number of events.

* $p = .054$.

drugs assumed, so we cannot analyze the importance of such factors on the outcomes. Moreover, we should consider that some patients may have masked and not declared the assumption of one drug. However, examining clinical records, we considered as “drug assumer” only subjects who declared to have continuously assumed the drug, following the criteria described above. Another important issue to be considered is represented by the fact that in the present study we cannot consider analytically the impact of oral hygiene on determining the increase of the risk for implant failure and peri-implantitis, although insufficient oral hygiene (and consequently plaque accumulation) could be associated with peri-implant tissue inflammation (Corbella et al., 2011; Schwarz et al., 2018; Serino & Strom, 2009); however we should consider that the subjects included were included in one oral hygiene program that implied yearly recall. Despite the here mentioned limitations, in the opinion of the Authors, the study has the strength of a representative sample, and of being one of the few studies accounting for the influence of several drug assumption on the outcomes, with a particular and specific focus on it. Moreover, statistical methods (patient-level survival analysis, as recommended in 2012 by Sanz et al. [2012], and

adjustment for number of implants per patient) provided more reliability to the results, although survival analysis could have overestimated the data about failures and peri-implantitis, as compared to prevalence studies.

In conclusion, the study found that the curve of occurrence of peri-implantitis in subjects assuming NSAIDs is significantly different as compared to the curve of controls. The use of PPIs, SSRIs, and antihypertensive medications appeared to have no influence on implant survival and on increasing the risk of peri-implantitis. More studies, with larger sample size and precise description of the administration patterns, could be useful to understand the role that several common medications might play in influencing the outcomes of dental implant treatments. The control of known risk factors (such as smoking and periodontitis) continues to have an important role in the prevention of peri-implantitis and implant failure.

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AUTHOR CONTRIBUTIONS

Stefano Corbella: Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Paolo Morandi:** Data curation (equal); investigation (equal); writing – original draft (equal). **Alice Alberti:** Data curation (equal); investigation (equal); writing – original draft (equal). **Benedetta Morandi:** Data curation (equal); investigation (equal); writing – original draft (equal). **Luca Francetti:** Conceptualization (equal); methodology (equal); writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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