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ORIGINAL ARTICLE

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Clinical benefits of systemic amoxicillin/metronidazole may depend on periodontitis stage and grade: An exploratory sub-analysis of the ABPARO trial

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Abstract

Aim: Assessment of treatment response after systemic amoxicillin/metronidazole adjunctive to subgingival instrumentation (SI) according to stages and grades of the 2018 classification of periodontal diseases.

Materials and Methods: We carried out exploratory re-analysis of the placebo-controlled, multi-centre ABPARO trial (52; 45/60 years of age; 205 males, 114 active smokers). Patients were randomized to SI with systemic amoxicillin 500 mg/metronidazole 400 mg (three times a day for 7 days, $n = 205$; ANTI) or placebo ($n = 200$; PLAC) and maintenance therapy every 3 months. Patients were reclassified according to the 2018 classification (stage/extent/grade). Treatment effect was the percentage of sites per patient with new attachment loss ≥1.3 mm (PSAL ≥ 1.3 mm) at 27.5 months post-baseline/randomization.

Results: All patients were assigned according to the stage ($n = 49$ localized stage III, $n = 206$ generalized stage III, $n = 150$ stage IV). Because of missing radiographs, only 222 patients were assigned to grades ($n = 73$ B, $n = 149$ C). Treatment (PLAC/ANTI) resulted in PSAL ≥ 1.3 mm (median; lower/upper quartile) in localized stage III (PLAC: 5.7; 3.3/8.4% vs. ANTI: 4.9; 3.0/8.3%; $p = .749$), generalized stage III (8.0; 4.5/14.3% vs. 4.7; 2.4/9.0%; $p < .001$), stage IV (8.5; 5.1/14.4% vs. 5.7; 3.3/10.6%; $p = .008$), grade B (4.4; 2.4/6.7% vs. 3.6; 1.9/4.7%; $p = .151$) and grade C (9.4; 5.3/14.3% vs. 4.8; 2.5/9.4%; $p < .001$).

Conclusions: In generalized periodontitis stage III/grade C, a clinically relevant lower percentage of disease progression after adjunctive systemic amoxicillin/metronidazole was observed compared to placebo (PLAC: 9.7; 5.8/14.3% vs. ANTI: 4.7; 2.4/9.0%; $p < .001$).

Peter Eickholz, Raphael Koch, Inga Harks and Benjamin Ehmke contributed equally to this work.

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amoxicillin/metronidazole, grade, periodontitis, stage, systemic antimicrobials

Clinical Relevance

Scientific rationale for study: Systemic amoxicillin and metronidazole are established adjuncts for subgingival instrumentation (SI). Aggressive periodontitis, the baseline percentage of sites with a pocket probing depth ≥5 mm, and age have been identified as indicators for antimicrobial use before the publication of the 2018 classification of periodontal diseases and conditions. The 2018 classification's stage/extent/grade system may provide similar indications for the decision for or against adjunctive antimicrobials.

Principal findings: A clinically relevant benefit for systemic amoxicillin and metronidazole adjunctive to SI over placebo was observed in patients with generalized stage III and grade C periodontitis regarding less additional clinical attachment loss.

Practical implications: Periodontitis stage, extent and grade could be used to select patients who might benefit from systemic antibiotics adjunctive to SI. Clinicians treating patients represented by the population in this sub-analysis might consider the reported stage, extent and grade as an aid when deciding for or against systemic amoxicillin/metronidazole use.

1 | INTRODUCTION

Subgingival instrumentation (SI) with adjunctive use of systemic antibiotics generally provides better clinical treatment results than SI alone (Teughels et al., 2020). However, the European Federation of Periodontology (EFP) S3 Level Clinical Practice Guideline for treating stage I to III periodontitis does not recommend the routine use of systemic antibiotics as an adjunct to SI in patients with periodontitis because of concerns about the impact of systemic antibiotic use on patients' and public health. After weighing benefits and possible adverse events, the adjunctive use of specific systemic antibiotics may be considered for particular patient categories (e.g., generalized periodontitis stage III and IV in young adults; Sanz et al., 2020; Kebschull et al., 2020).

Our large multi-centre, randomized controlled trial (RCT) comparing SI with adjunctive systemic amoxicillin and metronidazole or placebo for treating moderate to severe periodontitis (the ABPARO trial) observed noticeably better clinical results regarding additional clinical attachment loss (CAL) despite periodontal treatment, reduction of pocket probing depth (PPD) and 'treat-to-target' endpoints (≤4 sites with PPD ≥ 5 mm; Feres et al., 2020, Harks et al., 2015) in the antimicrobial group. However, the main clinical endpoint (per-patient percentage of sites with new clinical attachment loss [PSAL] ≥ 1.3 mm between baseline and 27.5 months) failed to reach clinical relevance despite achieving statistical significance (planning assumptions: placebo [PLAC] = 15%; antimicrobials [ANTI] = 7%; Harks et al., 2015). The threshold for clinical relevance was considered a reduction in PSAL ≥ 1.3 mm of >50% in the ANTI group compared with the PLAC group between randomization and 27.5 months (Greenstein & Lamster, 2000; Harks et al., 2014).

An exploratory analysis of the ABPARO data found clinical- and patient-related thresholds (age <55 years and ≥35% sites with PPD ≥ 5 mm at baseline) helpful for identifying patients who achieve a clinically relevant benefit from SI with adjunctive amoxicillin and metronidazole (median PSAL ≥ 1.3 mm: PLAC = 12%; ANTI = 4%; Eickholz et al., 2019). An S3 Level Clinical Practice Guideline from the German Society of Periodontology used the respective thresholds for recommendations regarding the adjunctive use of systemic antibiotics in SI (Jockel-Schneider et al., 2018; Pretzl et al., 2019). Unfortunately, the original and exploratory analyses used diagnoses based on the 1999 Classification of Periodontal Diseases and Conditions (Armitage, 1999), as did the clinical guideline. After the publication of the 2018 Classification of Periodontal and Peri-implant Diseases and Conditions, it makes sense to explore whether the stage, extent and grade system might provide criteria for deciding whether or not to use systemic antibiotics adjunctively to SI. This approach might enable the clinician to conclude the potential benefit of using adjunctive systemic antibiotics directly from the diagnosis.

This exploratory analysis of a large multi-centre trial aims to identify criteria in the 2018 Classification of Periodontal and Peri-implant Diseases and Conditions for which adjunctive antimicrobial use is associated with better clinical outcomes. We hypothesized that generalized stage III and IV in combination with grade C would receive greater benefits from the adjunctive use of metronidazole and amoxicillin.

2 | PATIENTS AND METHODS

2.1 | Study design

This was an exploratory re-analysis of the prospective, randomized, stratified, double-blind, multi-centre ABPARO trial (Clinical Trials.gov: NCT00707369) over 27.5 months (Eickholz et al., 2019; Harks et al., 2014, 2015). The analysis included all patients with a relative attachment level (RAL) measurement at 27.5 months after baseline examination/

randomization and baseline data to determine the stage and extent. The initial trial examined the effect of systemic amoxicillin (500 mg) and metronidazole (400 mg; intended thrice daily for 7 days) adjunctive to mechanical SI using clinical parameters in patients with moderate to severe periodontitis. Antimicrobials were prescribed empirically (i.e., without prior analysis of intra-oral bacteria; Eickholz et al., 2019; Harks et al., 2015, 2014). Therefore, only a brief description is provided below.

Patients aged 18–75 years with untreated moderate to severe chronic and aggressive periodontitis were included in the ABPARO trial. The key clinical inclusion criteria were ≥10 natural teeth in situ and PPDs of ≥6 mm in at least four teeth. The key exclusion criteria were confirmed or assumed allergies or former hypersensitive skin reactions to amoxicillin and/or metronidazole, systemic medications affecting periodontal health, and pregnancy. The institutional review boards of the participating centres approved the protocol, and all patients provided written informed consent. Moreover, an independent data and safety monitoring board reviewed the safety data throughout the trial. For stratification and balancing purposes, the patient population of the clinic of Münster university had been analysed according to the severity of periodontitis, and the median for sites with PPD ≥ 6 mm had been determined to be 38% (Harks et al., 2014). This stratification was done to avoid imbalances between the antibiotics and the placebo groups concerning periodontal disease severity. This ensured that in both groups the disease severity of the patients was comparable. The 38% cut-off was only used for balancing the groups and was not applied to the reclassification according to the 2018 classification done in this study. Patients were randomly assigned per centre in a 1:1 ratio using block randomization (size = 4) stratified by four strata according to severity and smoking to treatment with antimicrobials or placebo.

2.2 | Examinations and endpoints

At baseline, patients were asked to self-report smoking (non-smoker; smoker at <1, 1, 2 or >2 packs/day), and non-fasting blood samples were drawn to determine their haemoglobin A1c (HbA1c) levels (Harks et al., 2014, 2015).

All measurements were taken by blinded and calibrated examiners not involved in therapy (Harks et al., 2014, 2015). The examiner calibration was performed continuously throughout the study to minimize RAL measurements' intra- and inter-examiner variability (Grossi et al., 1996). Intra-examiner calibration started with a 1–3-month training before the measurements (visit 2) to familiarize them with the Florida Disk Probe handpiece (Florida Probe, Gainesville, FL, USA). This training aimed to achieve an intra-examiner reproducibility of ≥75% of measurements with total agreement and ≥95% within ±1 mm. After attaining this level of reproducibility, the inter-examiner calibration was conducted on manikins according to the 'gold standard'. The inter-examiner calibration was conducted in each centre on the same pair of manikins (32 examiners were involved in this study at different times). Therefore, the project manager (I.H.) travelled to each participating centre at baseline and after 12 and 24 months. Only examiners fulfilling the above-stated criteria passed the inter-examiner calibration (Harks et al., 2014).

Full-mouth periodontal measurements were performed at six sites for each tooth: primarily RAL measurements, corresponding to the distance from the occlusal surface to the bottom of the periodontal pocket (Florida Disk Probe). RAL was measured in two courses, and the mean of the two measurements per site was calculated for further analysis. The differences between baseline (randomization visit) and 27.5-month RAL readings revealed changes to the clinical attachment level (gain or loss of tooth-supporting tissue). The main outcome was the per-patient PSAL ≥ 1.3 mm between the baseline/randomization visit and the visit after 27.5 months. The outcomes explored included PPD, attachment level (sum of gingival recession and PPD) and gingival bleeding on probing (BOP) (Lang et al., 1990). BOP was determined approximately 30 s after the first course of RAL measurements (separately for buccal and lingual surfaces). The measurements of PPD and recession were made with a standard Florida Probe handpiece. The probe was inserted into the periodontal pocket between the tooth and gingiva. Then, the tube surrounding the probe was moved to the gingival margin to measure PPD and to the cementoenamel junction or restoration margin to measure recession. CAL was calculated by adding PPD and recession. Measurements of furcation involvement were performed using a manual furcation probe (Nabers Probe; PQ2N, HuFriedy, Chicago, USA). These parameters were used to define a clinical rationale for prescribing adjunctive systemic antimicrobials.

2.3 | Periodontal therapy

Each patient received 12 examinations and/or therapy visits over the 27.5-month study period. After the randomization examination (baseline; visit 2), patients received supra- and sub-gingival debridement in up to two sessions on two consecutive days. All mechanical therapy was performed with hand instruments and/or machine-driven scalers. Upon completion of the mechanical debridement, the antimicrobial group (ANTI) received empiric antimicrobials (amoxicillin trihydrate 574 mg: amoxicillin-ratiopharm 500 mg, Ratiopharm, Germany; metronidazole 400 mg: Flagyl 400, Sanofi-Aventis, Germany) and the placebo group (PLAC) received placebo pills, each taken thrice daily for 7 days. The medications were repackaged in neutral capsules so that they would appear identical. All patients were prescribed mouth rinse (0.2% chlorhexidine-digluconate, twice daily for 7 days) to prevent superinfection in the oral cavity. Patients were re-evaluated at least 2 months after mechanical debridement. Then, all patients received maintenance therapy, including full-mouth supra-gingival debridement and oral hygiene instruction at 3-month intervals. Sites with PPD ≥ 4 mm also received subgingival re-debridement.

2.4 | Periodontitis reclassification according to the 2018 classification

One author (M.G.) travelled to all centres and performed scans of the respective baseline radiographs (obtained at baseline/randomization visit or ≤12 months earlier) of patients included in the

ABPARO trial with 600 dpi resolution and 8-bit grey values. The images were stored as TIFF files and later analysed using the SIDEXIS neXt Generation software (version 2.4; Dentsply Sirona, Bensheim, Germany). Before analysing the radiographs, the ABPARO investigator at the Frankfurt centre (P.E.) calibrated M.G. First, P.E. analysed five panoramic and five sets of periapical radiographs unrelated to the ABPARO trial for bone loss/age index. Then, M.G. conducted the same analysis.

Information for determining stage and extent (localized <30% and generalized ≥30% of teeth) was present in the ABPARO trial data generated by baseline Florida probe measurements (severity: inter-dental CAL and missing teeth; complexity: PPD and furcation involvement) (Papapanou et al., 2018; Tonetti et al., 2018). Third molars were excluded in all analyses, calculations and stage/extent classification. All other teeth missing at randomization were considered as missing due to periodontal reasons.

The grade was assigned based on indirect evidence of disease progression using the assessment of bone loss/age index (Papapanou et al., 2018; Tonetti et al., 2018). The distances from the cementoenamel junction/restoration margin to the alveolar crest and root apex were measured for the most affected tooth using the measurement tool SIDEXIS. The quotient of both distances is the bone loss relative to root length in percent. Bone loss relative to root length (%) was divided by the patient's age to provide a bone loss/age index (grade A: <0.25; B: 0.25–1.0; C: >1.0).

In addition, smoking (grade A: non-smoker; B: <1 pack/day; C: ≥1 pack/day) and diabetic status (grade A: no self-reported diabetes; B: HbA1c < 7.0 and self-reported diabetes; C: HbA1c ≥ 7.0 and self-reported diabetes) were considered. Baseline HbA1c had been assessed for all patients. However, HbA1c was used to assign grade B or C only in patients with self-reported diabetes. The primary criterion was the bone loss/age index. The respective grade could then be upgraded by smoking or diabetes status. Self-reported smoking and diabetes status had been assessed before treatment (Harks et al., 2015).

2.5 | Statistical analysis

Standard univariate statistical analyses were used. Categorical variables are presented as absolute and relative frequencies. Continuous variables are presented as median (25%/75% quantile; interquartile range [IQR]). Treatment groups were compared within each stage, grade or stage/grade combination using Mann–Whitney *U* tests for continuous variables and Fisher's exact tests for categorical variables.

The main outcome for evaluating the treatment effect was the per-patient PSAL ≥ 1.3 mm between baseline measurement/randomization and 27.5 months. Additionally, mean PPD, recession and attachment level (all in millimetres) were calculated for each patient using the mean of all sites. For each patient, the mean changes in attachment level, PPD and recession over time were determined by calculating the difference (in millimetres) at each site between the time points and then averaging them. BOP (%) and plaque (%) were determined as the percentage of sites per patient with BOP or plaque. For each patient, changes were calculated as the difference in these percentages.

In addition, based on the comparison of ranks in each stage and grade, an empirical probability was calculated for the case where a randomly chosen patient from the ANTI group had a smaller PSAL ≥ 1.3 mm than a randomly chosen patient from the PLAC group (P[ANTI < PLAC]). To adjust for sex and age, a multivariable quantile regression (median) was fitted in the stage collective, with the main effects of sex, age, treatment group, stage and the interaction term between treatment group and stage included as influencing factors. The analysis was repeated for the grade collective by replacing stage by grade in the model.

Statistical analyses were performed using SAS software (version 9.4 of the SAS System for Windows; SAS Institute, Cary, NC, USA). All *p*-values and confidence intervals were two-sided and intended to be exploratory, not confirmatory. Therefore, no adjustment was made for multiple testing. Exploratory two-sided *p*-values ≤.05 were considered statistically noticeable.

3 | RESULTS

3.1 | Patients

From 506 randomized patients, 405 with available RAL measurements at 27.5 months and available stage determination were included in the analyses (PLAC: $n = 200$, ANTI: $n = 205$). The treatment groups were determined according to the intention-to-treat principle (as randomized). Radiographs were available to assign a grade for only 222 of these patients. The distributions of stages and grades and baseline demographic characteristics in the PLAC and ANTI groups are provided in Tables 1–3. Grades were evenly distributed across all stages in both treatment groups (Table 1). At baseline, age differed between stages ($p < .001$), with stage IV patients being the oldest (median = 56 [IQR: 49/62] years), followed by localized (<30% of teeth) stage III patients (53 [45/58] years), and generalized (≥30% of teeth) stage III patients being the youngest (49 [43/57] years). Diabetes mellitus was more common in stage IV patients ($n = 13$ [9%]) than in localized stage III ($n = 1$ [2%]) and generalized stage III ($n = 5$ [2%]) patients ($p = .020$).

The grade was assigned by indirect evidence of disease progression (bone loss/age index) after evaluating complete sets of periapical baseline radiographs from 119 patients and panoramic radiographs from 103 patients. At baseline, grade C patients were younger (49 [44/55] years) and more frequent smokers ($n = 52$ [36.4%]) than grade B patients (age: 58 [49/65], $p < .001$; smokers: $n = 9$ [11.3%], $p < .001$). Grade C was assigned to three patients (two in PLAC and one in ANTI) because of heavy smoking and two patients (both ANTI) because of HbA1c ≥ 7%. Table 2 (by stage) and Table 3 (by grade) provide the patient characteristics at baseline in each treatment group.

TABLE 1 Baseline diagnoses: Periodontitis according to treatment group, stage, extent and grade ($n = 405$).

Placebo (PLAC) ($n = 200$)					
Stage		**No radiographs**	**Grade B**	**Grade C**	**Total**
III localized	*n*	8	9	7	24
	% within stage	33.3%	37.5%	29.2%	100.0%
	% within grade	9.0%	22.5%	9.9%	12.0%
III generalized	*n*	52	17	37	106
	% within stage	49.1%	16.0%	34.9%	100.0%
	% within grade	58.4%	42.5%	52.1%	53.0%
IV	*n*	29	14	27	70
	% within stage	41.4%	20.0%	38.6%	100.0%
	% within grade	32.6%	35.0%	38.0%	35.0%
Total	*n*	89	40	71	200
	% within stage	44.5%	20.0%	35.5%	100.0%
Antimicrobial (ANTI) ($n = 205$)					
Stage		**No radiographs**	**Grade B**	**Grade C**	**Total**
III localized	*n*	11	8	6	25
	% within stage	44.0%	32.0%	24.0%	100.0%
	% within grade	11.7%	24.2%	7.7%	12.2%
III generalized	*n*	49	10	41	100
	% within stage	49.0%	10.0%	41.0%	100.0%
	% within grade	52.1%	30.3%	52.6%	48.8%
IV	*n*	34	15	31	80
	% within stage	42.5%	18.8%	38.8%	100.0%
	% within grade	36.2%	45.5%	39.7%	39.0%
Total	*n*	94	33	78	205
	% within stage	45.9%	16.1%	38.0%	100.0%

Note: Results are reported as frequencies (*n*) or percentages (%) within each grade or stage category for each treatment group separately.

3.2 | Rater agreement

Ten sets of radiographs (five panoramic and five sets of periapical radiographs) from 10 patients unrelated to the ABPARO trial were used to calibrate the investigator (M.G.) who assessed grade by relative bone loss/age coefficient. The local principal investigator of the Frankfurt centre (P.E.) and M.G. independently assigned grades using the 10 sets of radiographs. P.E. judged the same tooth as having the most severe relative bone loss as M.G. in five patients (50%). Nevertheless, the respective mean bone loss/age index was similar for both examiners across all 10 patients (P.E.: 1.45; M.G.: 1.40). Furthermore, the assigned periodontitis grades agreed perfectly between P.E. and M.G. across all 10 patients (two grade B and eight grade C).

3.3 | Treatment effect regarding stage

Patients with localized stage III periodontitis showed no benefit from systemic antimicrobials in PSAL ≥ 1.3 mm at 27.5 months after SI. However, systemic antimicrobials resulted in lower PSAL ≥ 1.3 mm in patients with generalized stage III (PLAC: 8.0 [4.5/14.3]; ANTI: 4.7 [2.4/9.0]; $p < .001$) and stage IV (PLAC: 8.5 [5.1/14.4]; ANTI: 5.7 [3.3/10.6]; $p = .008$) periodontitis (Table 4). Mean PPD and percentage of sites with PPD ≥ 5 mm showed the greatest reductions with systemic antimicrobials in patients with generalized stage III and stage IV periodontitis (Table 5). The number of patients achieving ≤4 sites with PPD ≥ 5 mm differed most between treatment groups for generalized stage III periodontitis.

3.4 | Treatment effect regarding grade

In patients with grade B periodontitis, systemic antimicrobials failed to result in a statistically noticeable benefit with regard to PSAL ≥ 1.3 mm at 27.5 months after SI. However, systemic antimicrobials resulted in fewer sites with progressing CAL in grade C (Table 4). Regarding median PPD reduction and patients who reached the 'treat-to-target' endpoint (≤4 sites with PPD ≥ 5 mm) (Feres et al., 2020), the greatest benefit was also observed for grade C (PLAC: 39%; ANTI: 69%; Table 6).

TABLE 2 Patient characteristics at baseline according to stage and extent.

Stage	Localized III			Generalized III			IV		
	Placebo (PLAC) (n = 24)	Antimicrobial (ANTI) (n = 25)	p-Value	Placebo (PLAC) (n = 106)	Antimicrobial (ANTI) (n = 100)	p-Value	Placebo (PLAC) (n = 70)	Antimicrobial (ANTI) (n = 80)	p-Value
Male, n (%)	11 (51.7)	10 (40)	.776**	55 (52)	51 (51)	1.000**	28 (54)	40 (50)	.398**
Age (years), median (IQR)	52.0 (44.0, 57.0)	53.0 (46.0, 59.0)	.818*	49.0 (42.0, 57.0)	49.0 (43.5, 57.5)	.549*	54.0 (47.0, 63.0)	56.0 (50.0, 62.0)	.398*
BMI (kg/m^2), median (IQR)	25.4 (23.3, 29.3)	25.2 (23.0, 28.4)	.509*	25.2 (22.1, 27.7)	24.5 (22.5, 26.8)	.464*	25.3 (23.3, 28.7)	24.9 (22.8, 28.3)	.712*
Smoker, n (%)	2 (8)	6 (24)	.818**	29 (27)	29 (29)	.877*	22 (31)	26 (33)	1.000*
Diabetes, n (%)	0 (0)	1 (4)	1.000**	3 (3)	2 (2)	1.000**	7 (10)	6 (8)	.772**

Note: Results are shown as median an interquartile range (IQR, 25% quantile, 75% quantile) or frequencies (n) and percentages (%) within each stage and treatment group. *p-Values are from two-sided Mann–Whitney U test comparing the two treatment groups. **p-Value from Fisher's exact test.
Abbreviation: BMI, body mass index.

The empirical rank-based probability that an ANTI patient had a lower PSAL > 1.3 mm than a PLAC patient was highest for generalized stage III in combination with grade C (74.3%; Figure 1; Table 4).

The results of the sex- and age-adjusted quantile regressions confirm the univariate findings and can be found in Tables S1 and S2.

4 | DISCUSSION

This exploratory analysis of the placebo-controlled, multi-centre ABPARO trial (Eickholz et al., 2016; Hagenfeld et al., 2020; Harks et al., 2014, 2015; Kocher et al., 2019) aimed to investigate whether the stage/extent/grade system of the 2018 Classification of Periodontal and Peri-implant Diseases and Conditions (Papapanou et al., 2018; Tonetti et al., 2018) provides indications for the use of systemic amoxicillin/metronidazole adjunctive to SI. Except for localized stage III, grade B (PLAC: 3.3% [3.1%/4.9%]; ANTI: 3.7% [2.1%/5.7%]; $p = .885$), antimicrobials resulted in lower median PSAL ≥ 1.3 mm for localized stage III, grade C (PLAC: 6.4% [4.9%/11.7%]; ANTI: 4.3% [1.9%/8.3%]; $p = .520$); generalized stage III, grade B (PLAC: 5.3% [2.4%/6.8%]; ANTI: 3.0% [1.9%/4.5%]; $p = .269$); generalized stage III, grade C (PLAC: 9.7% [5.8%/14.3%]; ANTI: 4.7% [2.4%/9.0%]; $p < .001$); stage IV, grade B (PLAC: 4.8% [3.1%/6.3%]; ANTI: 3.8% [1.9%/4.2%]; $p = .348$); and stage IV, grade C (PLAC: 8.3% [5.3%/16.7%]; ANTI: 5.3% [3.3%/12.5%]; $p = .049$; Table 4; Figure 1). In generalized stage III combined with grade C periodontitis, a clinically relevant benefit was observed with adjunctive systemic amoxicillin/metronidazole compared with placebo.

A diagnosis must be established before treatment. This exploratory analysis identified specific diagnoses (i.e., periodontitis generalized stage III, grade C) according to the 2018 classification that have gained clinically relevant benefits from systemic amoxicillin and metronidazole adjunctive to SI compared to the other diagnoses. Therefore, a periodontal diagnosis according to the 2018 classification provides criteria to support a decision on systemic antibiotics adjunctive to SI. Therefore, the suggested diagnosis-based strategy to determine whether or not to prescribe adjunctive antimicrobials can easily be adapted to a clinician's daily routine without additional effort. However, this diagnosis-based approach should be seen only as a helpful orientation and by no means a strict rule for antimicrobial use because the variation of our data indicates that individual patients with different diagnoses may or may not benefit.

Patients with stage IV periodontitis were, on average, older than those with generalized stage III (Table 2). Since stage IV is due to ≥5 teeth missing, <20 teeth in total or <10 pairs of teeth in occlusion, it is associated with tooth loss. This association can easily be explained by age as a strong predictor for tooth loss (Chambrone & Chambrone, 2006; Eickholz et al., 2008; Leung et al., 2006). Patients with grade C were, on average, younger than those with grade B. Because of missing primary evidence of progression (i.e., longitudinal attachment or bone loss over 5 years), the grade was assessed in most patients using bone loss/age quotient (radiographic bone loss at the most severely affected tooth relative to root length

TABLE 3 Patient characteristics at baseline according to grade.

Grade	No radiographs (missing)			B			C		
	Placebo (PLAC) ($n = 89$)	Antimicrobial (ANTI) ($n = 94$)	*p*-Value	Placebo (PLAC) ($n = 40$)	Antimicrobial (ANTI) ($n = 33$)	*p*-Value	Placebo (PLAC) ($n = 71$)	Antimicrobial (ANTI) ($n = 78$)	*p*-Value
Male, *n* (%)	44 (49)	52 (55)	.461**	24 (60)	13 (39)	.102**	36 (51)	36 (46)	.624**
Age (years), median (IQR)	51.0 (44.0, 60.0)	52.5 (47.0, 62.0)	.153*	58.0 (47.5, 63.5)	58.0 (51.0, 65.0)	.820*	49.0 (43.0, 54.0)	49.0 (45.0, 57.0)	.447*
BMI (kg/m^2), median (IQR)	24.8 (21.9, 28.0)	24.7 (23.0, 27.4)	.820*	26.0 (24.0, 29.8)	25.2 (23.8, 26.6)	.127*	25.3 (22.3, 28.3)	24.0 (22.0, 28.4)	.442*
Smoker, *n* (%)	27 (30)	26 (28)	.746**	4 (10)	5 (15)	.723*	22 (31)	30 (39)	.391*
Diabetes, *n* (%)	4 (4)	4 (4)	1.000**	4 (10)	0 (0)	.122**	2 (3)	5 (6)	.446**

Note: Results are shown as median an interquartile range (IQR, 25% quantile, 75% quantile) or frequencies (*n*) and percentages (%) within each grade and treatment group. *p-Value from two-sided Mann–Whitney U test comparing the two treatment groups; **p-Value from Fisher's exact test.
Abbreviation: BMI, body mass index.

divided by age) (Tonetti et al., 2018). Grade C was assigned only for three patients (two in PLAC and one in ANTI) due to heavy smoking and two (both ANTI) due to HbA1c ≥ 7%. Therefore, age also plays an important role in the grade assignment. The younger the patient, the more likely the bone loss/age quotient will reach 1.0, the threshold for grade C (Tonetti et al., 2018).

The threshold-related strategy (age and percentage of sites with PPD ≥ 5 mm) found young patients (age ≤35 years) suffering from severe periodontitis (Eickholz et al., 2019; Pretzl et al., 2019) to benefit more from systemic antimicrobials than older patients. Furthermore, patients with formerly called 'chronic' periodontitis aged <56 years and with PPD ≥ 5 mm at ≥35% of all sites had better clinical results (smaller PSAL ≥ 1.3 mm) than patients aged ≥56 years or with less deep pockets (Eickholz et al., 2019; Pretzl et al., 2019). Age also played an important role in the threshold-related strategy. However, in patients with 'chronic' periodontitis, severity (with ≥35% sites with PPD ≥ 5 mm) was another factor represented in the diagnosis-based strategy by stage (deep pockets) and extent (percentage of sites). Nevertheless, while the threshold-related strategy requires calculating the percentage of sites with PPD ≥ 5 mm, the diagnosis-based strategy requires only a proper diagnosis according to the 2018 classification, an existing prerequisite of periodontal treatment.

The percentage of patients who were smokers and or suffering from diabetes was also higher for grade C than for grade B, likely due to the assignment of grade C to heavy smokers (≥10 cigarettes/day; Tonetti et al., 2018; ≥1 pack/day in this analysis) and patients with uncontrolled diabetes (HbA1c ≥ 7%). Therefore, in the diagnosis-based approach, smoking and diabetes affect the decision regarding systemic antimicrobials by grade. However, the number of patients with diabetes was small, and grade C was assigned only to two patients based on HbA1c ≥ 7%.

The main effect of adjunctive systemic antimicrobials is a greater reduction in deep pocket sites than mechanical therapy alone (Mombelli et al., 2015; Silva et al., 2011). Fewer deep pockets after therapy may reduce the need for surgery and ease maintenance therapy because more teeth with residual deep pockets would plausibly require a more laborious maintenance therapy. In this study, the PSAL results differed significantly ($p < .05$) between the ANTI and PLAC groups in patients with generalized stage III (ANTI: 4.7% [2.4%/9.0%]; PLAC: 8.0% [4.5%/14.3%]) and stage IV (ANTI: 5.7% [3.3%/10.6%]; PLAC: 8.5% [5.1%/14.4%]; Table 4; Figure 1). However, regarding the main clinical endpoint (PSAL ≥ 1.3 mm) between baseline and 27.5 months, the benefit failed to reach the originally defined assumptions for clinical relevance (PLAC: 15%; ANTI: 7%; Harks et al., 2015). The difference in median PSAL ≥ 1.3 mm between ANTI and PLAC for patients with localized stage III was 0.8%. Such a small difference cannot be considered clinically relevant (Table 4; Figure 1). ANTI resulted in PSAL ≥ 1.3 mm of 4.7% (2.4%/9.0%) and PLAC in PSAL ≥ 1.3 mm of 9.7% (5.8%/14.3%) in patients with generalized stage III and grade C periodontitis (Figure 1). Therefore, the incidence of additional CAL 27.5 months after baseline measurement/randomization with antimicrobials was <50% of the incidence with placebo, thus achieving clinical relevance.

TABLE 4 Percentage of sites with new clinical attachment loss ≥1.3 mm between baseline and 27.5 months for stage, extent, grade and the stage/grade combination.

PSAL ≥ 1.3 mm (%) between baseline/randomization and 27.5 months				
	Treatment group			
	Placebo (PLAC)	Antimicrobial (ANTI)	*p*-Value	P(ANTI < PLAC)
Stage				
Localized III	$n = 24$	$n = 25$		
	5.7 (3.3, 8.4)	4.9 (3.0, 8.3)	.749	52.3%
Generalized III	$n = 106$	$n = 99$[a]		
	8.0 (4.5, 14.3)	4.7 (2.4, 9.0)	<.001	65.7%
IV	$n = 70$	$n = 80$		
	8.5 (5.1, 14.4)	5.7 (3.3, 10.6)	.008	62.2%
Grade				
No radiographs (missing)	$n = 89$	$n = 93$[a]		
	9.0 (5.2, 14.6)	5.9 (3.6, 10.2)	.007	61.4%
B	$n = 40$	$n = 33$		
	4.4 (2.4, 6.7)	3.6 (1.9, 4.7)	.151	59.1%
C	$n = 71$	$n = 78$		
	9.4 (5.3, 14.3)	4.8 (2.5, 9.4)	<.001	68.9%
Stage/grade				
Localized III/B	$n = 9$	$n = 8$		
	3.3 (3.1, 4.9)	3.7 (2.1, 5.7)	.885	52.8%
Localized III/C	$n = 7$	$n = 6$		
	6.4 (4.9, 11.7)	4.3 (1.9, 8.3)	.520	61.9%
Generalized III/B	$n = 17$	$n = 10$		
	5.3 (2.4, 6.8)	3.0 (1.9, 4.5)	.269	62.4%
Generalized III/C	$n = 37$	$n = 41$		
	9.7 (5.8, 14.3)	4.7 (2.4, 9.0)	<.001	74.3%
IV/B	$n = 14$	$n = 15$		
	4.8 (3.1, 6.3)	3.8 (1.9, 4.2)	.348	59.5%
IV/C	$n = 27$	$n = 31$		
	8.3 (5.3, 16.7)	5.3 (3.3, 12.5)	.049	65.0%

Note: Results are shown as frequencies (*n*), median (25% quantile, 75% quantile), and rank-based empirical probabilities P(ANTI < PLAC), that is, the probability that a randomly chosen patient from the antimicrobial group has a smaller PSAL ≥ 1.3 mm than a randomly chosen patient from the placebo group. *p*-Values used to compare the PLAC and antimicrobial group were obtained from Mann–Whitney *U* tests.
Abbreviation: PSAL, percentage of sites per patient showing new attachment loss.
[a]Missing baseline relative attachment level measurement for one patient.

Apart from the study by Ehmke et al. (2005), ABPARO is the only RCT on systemic antimicrobials adjunctive to SI using PSAL ≥ 1.3 mm as the main clinical outcome (Ehmke et al., 2005). Therefore, a comparison with other clinical trials regarding this clinical endpoint is impossible. However, the ABPARO trial did also score the proportion of 'treat-to-target' endpoint (i.e., ≤4 sites with PPDs ≥ 5 mm; Feres et al., 2020). The ABPARO trial reported higher frequencies of the 'treat-to-target' endpoint in the ANTI group (63.1%) than in the PLAC group (36.5%) 27.5 months after SI (Harks et al., 2015). This observation was confirmed by others (ANTI: 75%; PLAC: 25%; Tamashiro et al., 2016). The 'treat-to-target' endpoint was more common in the ANTI group than in the PLAC group among patients with generalized stage III and IV and grade C periodontitis. Amoxicillin (500 mg) and metronidazole (400 mg), thrice daily for 7 days, are widely prescribed adjunctively to SI (Cosgarea et al., 2022; Harks et al., 2015). A variation is the prescription of 500 instead of 400 mg of metronidazole thrice daily for 7 days with 500 mg of amoxicillin (Griffiths et al., 2011). Some groups prescribe this combination for 14 days (Faveri et al., 2014; Feres et al., 2012; Tamashiro et al., 2016). However, this longer period does not appear to result in higher percentages of 'treat-to-target' endpoints than 7 days at 2–3 months after SI (Faveri et al., 2014; Harks et al., 2015).

This study had several limitations. First, diagnoses could not be assigned to all patients according to the 2018 classification. Second,

TABLE 5 Patient clinical data at baseline and 27.5 months follow-up according to stage and extent.

Stage	Localized III			Generalized III			IV		
	Placebo (PLAC) ($n = 24$)	Antimicrobial (ANTI) ($n = 25$)	p-Value	Placebo (PLAC) ($n = 106$)	Antimicrobial (ANTI) ($n = 100$)	p-Value	Placebo (PLAC) ($n = 70$)	Antimicrobial (ANTI) ($n = 80$)	p-Value
Baseline, mean PPD (mm)	2.8 (2.7, 3.0)	2.7 (2.6, 3.0)	.711*	3.4 (3.1, 4.0)	3.4 (3.1, 3.8)	.558*	3.4 (2.9, 4.1)	3.6 (3.1, 4.1)	.303*
27.5 months, mean PPD (mm)	2.4 (2.0, 2.7)	2.1 (1.9, 2.4)	.047*	2.6 (2.3, 3.2)	2.2 (2.0, 2.6)	<.001*	2.4 (2.0, 3.0)	2.3 (2.1, 2.7)	.296*
Change	−0.4 (−0.7, −0.1)	−0.7 (−0.9, −0.3)	.131*	−0.8 (−1.3, −0.5)	−1.1 (−1.7, −0.7)	.001*	−0.9 (−1.4, −0.5)	−1.1 (−1.7, −0.6)	.157*
Baseline, mean CAL (mm)	3.1 (2.8, 3.3)	3.1 (2.7, 3.3)	0.697*	4.0 (3.6, 4.7)	3.9 (3.5, 4.5)	.221*	4.2 (3.5, 5.1)	4.2 (3.7, 4.8)	.708*
27.5 months, mean CAL (mm)	2.8 (2.3, 3.2)	2.5 (2.2, 2.7)	.084*	3.7 (3.0, 4.4)	3.2 (2.6, 3.9)	<.001*	3.6 (3.0, 4.4)	3.8 (3.2, 4.4)	.782*
Change	−0.2 (−0.6, 0.0)	−0.4 (−0.7, −0.3)	.131*	−0.3 (−0.9, 0.2)	−0.7 (−1.1, −0.2)	<.001*	−0.4 (−0.9, 0.0)	−0.6 (−0.9, −0.1)	.708*
Baseline, PPD ≥ 5 mm (%)	7.4 (4.8, 10.2)	8.0 (5.3, 8.7)	.818*	17.0 (11.9, 27.2)	17.0 (11.8, 26.0)	.622*	17.9 (9.8, 34.1)	21.3 (11.7, 30.5)	.505*
27.5 months, PPD ≥ 5 mm (%)	2.1 (0.3, 4.3)	0.6 (0.0, 1.9)	.019*	6.1 (2.4, 14.6)	2.0 (0.6, 6.1)	<.001*	5.1 (1.1, 13.1)	2.3 (0.8, 6.6)	.019*
Change	−5.2 (−6.6, −2.8)	−6.0 (−8.3, −4.2)	.084*	−10.1 (−18.5, −5.1)	−13.2 (−22.4, −8.7)	.011*	−11.1 (−23.0, −5.1)	−14.5 (−25.0, −6.1)	.159*
Baseline, BOP (%)	25.9 (19.9, 37.5)	25.9 (13.0, 46.0)	.375*	28.8 (13.5, 49.0)	36.6 (19.7, 51.0)[a]	.043*	38.6 (16.8, 66.0)	35.4 (18.4, 57.8)	.019*
27.5 months, BOP (%)	17.2 (9.0, 29.2)	6.5 (3.1, 46.0)	.375*	16.6 (7.2, 27.3)	10.3 (4.4, 17.0)	<.001*	15.4 (6.8, 27.2)	8.6 (3.6, 19.6)	.007*
Change	−9.9 (−30.3, 1.9)	−16.7 (−28.5, −1.1)	.441*	−12.6 (−28.2, −1.4)	−25.0 (−36.7, −8.8)[a]	.001*	−11.9 (−25.8, −7.1)	−18.7 (−37.3, −6.5)	.100*
Baseline, plaque (%)	26.8 (11.5, 48.7)	23.1 (13.5, 45.0)	.944*	26.0 (12.5, 48.2)	36.2 (20.9, 54.3)	.028*	44.0 (18.8, 65.3)	35.7 (18.5, 57.2)	.305*
27.5 months, plaque (%)	28.6 (21.4, 43.4)	27.1 (16.0, 44.6)	.596*	33.3 (17.9, 50.0)	32.9 (19.6, 53.9)	.746*	32.9 (18.8, 53.3)	39.6 (20.3, 61.3)	.235*
Change	7.3 (−4.5, 13.1)	0.0 (−14.8, 15.8)	.084*	1.6 (−12.2, 26.0)	−1.3 (−20.9, 13.7)	.625*	−4.1 (−21.6, 16.7)	4.4 (−16.5, 22.6)	.075*
Baseline, ≤4 sites with PPD ≥ 5 mm, n (%)	2 (8)	2 (8)	1.000**	0 (0)	1 (1)	.485**	0 (0)	1 (1)	1.000**
27.5 months, ≤4 sites with PPD ≥ 5 mm, n (%)	15 (63)	22 (88)	.051**	31 (29)	54 (57)	<.001**	34 (49)	54 (58)	.021**

Note: Results are reported as median (25% quantile, 75% quantile); *p-Values from two-sided Mann–Whitney U test comparing the two treatment groups; **p-Value from Fisher's exact test.
Abbreviations: BOP, bleeding on probing (percentage of sites per patient); CAL, clinical attachment level; PPD, pocket probing depth; PPD ≥ 5 mm, percentage of sites per patient with pocket probing depth ≥5 mm; PSAL, percentage of sites per patient showing new relative attachment loss.
[a]Missing for one patient.

TABLE 6 Patient clinical data at baseline and 27.5 months follow-up according to grade.

Grade	No radiographs			B			C		
	Placebo (PLAC) ($n = 89$)	Antimicrobial (ANTI) ($n = 94$)	p-Value	Placebo (PLAC) ($n = 40$)	Antimicrobial (ANTI) ($n = 33$)	p-Value	Placebo (PLAC) ($n = 71$)	Antimicrobial (ANTI) ($n = 78$)	p-Value
Baseline, mean PPD (mm)	3.3 (3.0, 4.1)	3.3 (3.0, 3.8)	.994*	3.1 (2.8, 3.5)	3.2 (2.8, 3.5)	.576*	3.4 (2.9, 4.1)	3.5 (3.0, 4.0)	.830*
27.5 months, mean PPD (mm)	2.8 (2.2, 3.3)	2.4 (2.1, 2.8)	.005*	2.2 (1.8, 2.6)	2.1 (1.7, 2.2)	.171*	2.5 (2.2, 2.9)	2.2 (2.0, 2.5)	<.001*
Change	−0.8 (−1.1, −0.3)	−0.9 (−1.6, −0.4)	.079*	−0.9 (−1.3, −0.4)	−1.1 (−1.6, −0.7)	.145*	−0.8 (−1.5, −0.5)	−1.2 (−1.6, −0.8)	.007*
Baseline, mean CAL (mm)	4.0 (3.5, 4.9)	4.0 (3.4, 4.6)	.414*	3.6 (3.0, 3.9)	3.5 (3.1, 3.9)	.987*	4.2 (3.4, 4.9)	4.1 (3.5, 4.7)	.745*
27.5 months, mean CAL (mm)	3.8 (3.1, 4.5)	3.4 (2.8, 4.2)	.009*	3.1 (2.6, 3.4)	2.9 (2.5, 3.3)	.435*	3.5 (2.9, 4.3)	3.3 (2.6, 4.0)	.113*
Change	−0.2 (−0.7, 0.1)	−0.6 (−1.0, 0.0)	.007*	−0.5 (−0.9, −0.2)	−0.4 (−1.0, −0.2)	.744*	−0.5 (−1.2, 0.0)	−0.7 (−1.0, −0.4)	.066*
Baseline, PPD ≥ 5 mm (%)	14.3 (10.8, 34.1)	16.7 (10.5, 27.0)	.904*	11.1 (7.2, 18.0)	13.2 (8.3, 19.6)	.626*	18.9 (11.1, 32.7)	18.7 (9.9, 27.8)	.613*
27.5 months, PPD ≥ 5 mm (%)	6.3 (2.5, 15.9)	2.5 (0.8, 7.7)	<.001*	2.1 (0.6, 4.0)	0.7 (0.0, 2.3)	.056*	5.6 (2.2, 11.6)	1.6 (0.0, 3.9)	<.001*
Change	−7.6 (−16.0, −3.6)	−10.5 (−23.0, −5.9)	.052*	−9.0 (−11.7, −4.6)	−10.1 (−18.6, −5.8)	.263*	−11.4 (−21.3, −5.8)	−14.1 (−23.7, −8.7)	.072*
Baseline, BOP (%)	31.2 (19.2, 46.5)	33.3 (25.9, 46.5)[a]	.149*	32.4 (20.6, 49.6)	34.0 (27.3, 54.9)	.520*	32.6 (24.0, 47.6)	30.2 (19.8, 45.7)	.347*
27.5 months, BOP (%)	21.6 (10.9, 31.7)	12.9 (5.6, 21.3)	<.001*	13.4 (7.2, 24.5)	6.2 (2.9, 17.9)	.030*	13.0 (5.9, 22.2)	6.5 (3.1, 11.8)	<.001*
Change	−9.5 (−21.9, −1.2)	−20.0 (−35.5, −3.3)[a]	.001*	−15.4 (−27.1, −6.9)	−22.2 (−34.7, −8.7)	.183*	−20.8 (−33.3, −7.0)	−23.6 (−37.2, −9.4)	.253*
Baseline, plaque (%)	26.0 (12.5, 52.9)	30.5 (16.7, 47.9)	.668*	30.8 (16.8, 59.7)	43.3 (30.4, 62.5)	.214*	34.4 (16.2, 47.8)	37.3 (18.2, 54.5)	.527*
27.5 months, plaque (%)	30.4 (17.7, 51.3)	31.8 (16.0, 52.9)	.822*	38.1 (26.0, 58.8)	47.9 (25.0, 61.9)	.686*	29.8 (17.0, 43.0)	34.5 (20.0, 52.4)	.151*
Change	3.6 (−12.2, 21.4)	0.9 (−14.9, 15.4)	.774*	7.3 (−19.0, 25.6)	3.4 (−27.1, 25.0)	.702*	−4.6 (−18.8, 9.2)	−0.8 (−18.8, 17.9)	.673*
Baseline, ≤4 sites with PPD ≥ 5 mm, n (%)	1 (1)	2 (2)	1.000**	1 (3)	2 (6)	.586**	0 (0)	0 (0)	-
27.5 months, ≤4 sites with PPD ≥ 5 mm, n (%)	26 (29)	53 (56)	<.001**	26 (65)	26 (79)	.299**	28 (39)	54 (69)	<.001**

Note: Results are reported as median (25% quantile, 75% quantile). *p-Value from two-sided Mann–Whitney U test comparing the two treatment groups. **p-Value from Fisher's exact test.
Abbreviations: BOP, bleeding on probing (percentage of sites per patient); CAL, clinical attachment level; PPD, pocket probing depth; PPD ≥ 5 mm, percentage of sites per patient with pocket probing depth ≥5 mm; PSAL, percentage of sites per patient showing new relative attachment loss.
[a]Missing for one patient.

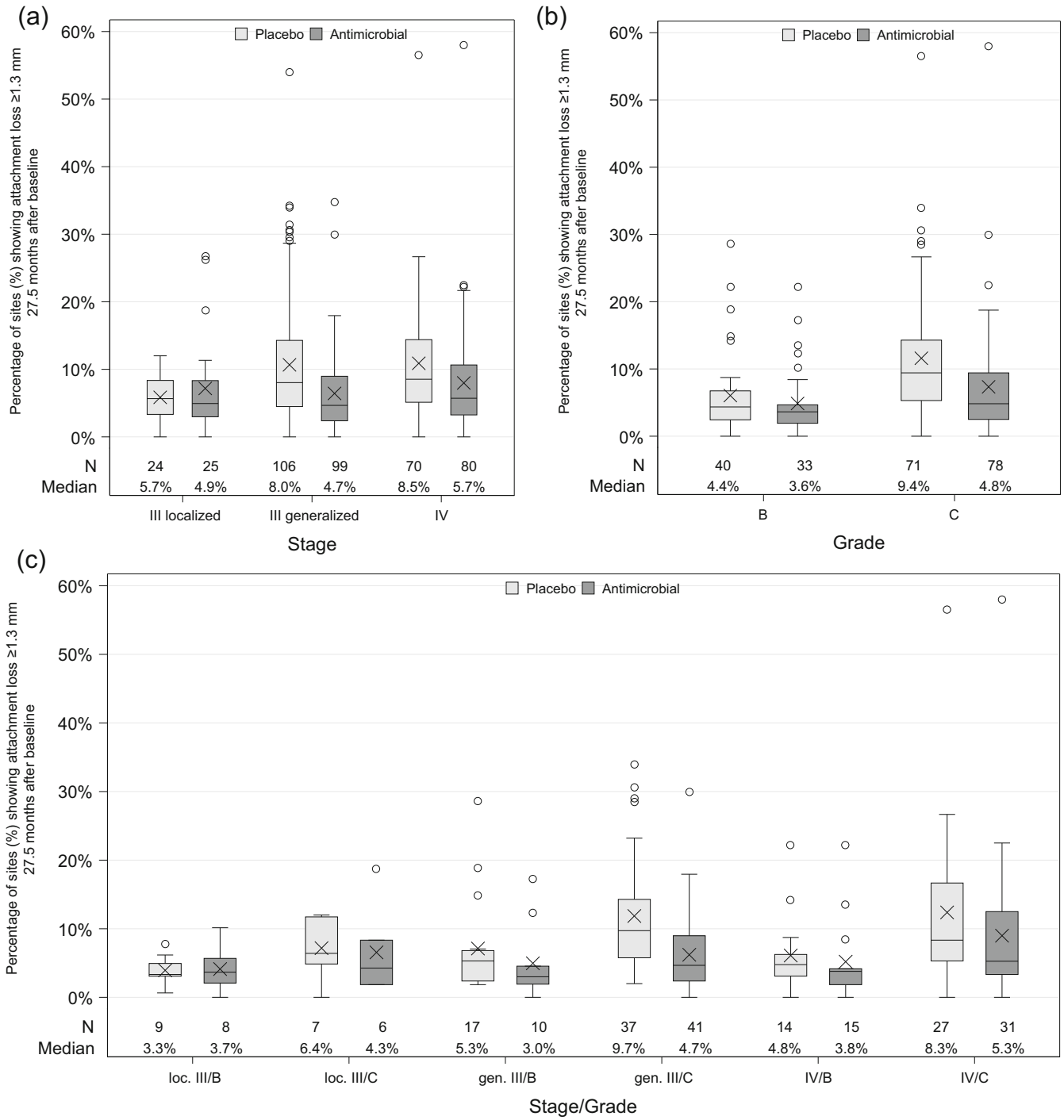

FIGURE 1 Boxplots of the percentage of sites per patient showing new relative attachment loss ≥1.3 mm between baseline/randomization and 27.5-month visit by treatment group and by stage and extent (a) ($n = 405$), by grade (b) ($n = 222$), and by the combination of stage and grade (c) ($n = 222$). The box represents the interquartile range (IQR), with the median indicated by a horizontal line inside the box. The whiskers extend to the most extreme data points within 1.5 times the IQR. Outliers, defined as data points beyond 1.5 times the IQR, are plotted as individual points. Marker X refers to the mean. The median and number (*N*) of each subgroup are reported below the boxplots.

the ABPARO trial assessed smoking not as the number of cigarettes per day but as cigarette packs per day. Therefore, heavy smoking associated with grade C was not assigned for ≥10 cigarettes/day but ≥1 pack/day. Third, patients were not asked at baseline which teeth were missing for periodontal or other reasons. Retrospectively, the reason for tooth loss could not be determined. Since all participants of the ABPARO trial suffered from at least localized stage III periodontitis, we hypothesized that all teeth were lost as a result of periodontitis. Therefore, we used the total number of missing teeth except for third molars as the discriminator

between stages III and IV, which may have introduced misclassification in some cases. However, other groups have applied this approach earlier (El Sayed et al., 2022; Graetz et al., 2019). Fourth, not all radiographs obtained at baseline could be retrieved because of the long time that had passed since the start of the study. Many clinics destroy patients' charts if they do not show up for 10 years. Therefore, a grade could not be assigned for 183 patients, weakening the conclusions regarding grade. Finally, sample sizes substantially decreased when splitting the entire cohort into six subgroups according to stage and grade and comparing ANTI and PLAC patients within each subgroup (Figure 1c). The tests for these comparisons have low power when the differences are small. However, except for generalized stage III periodontitis with grade C, none of the comparisons in the subgroups reached the threshold for clinical relevance.

Some of these limitations highlight the need for RCTs considering the 2018 Classification of Periodontal and Peri-implant Diseases and Conditions from their inception. These studies might include only specific diagnoses (e.g., stage IV or grade B) or, under ideal conditions, may stratify randomization to ANTI and PLAC according to stage and grade. However, the latter would require a relatively large total sample.

Against the background and danger of increasing microbial resistance, systemic antibiotics should be prescribed cautiously for treating non-life-threatening diseases. This attitude is clearly expressed by the EFP's clinical guidelines for treating stage I, II and III periodontitis (Sanz et al., 2020). The increased appearance of bacterial resistance is strongly associated with the frequency of antibiotic use (van Winkelhoff et al., 2005). Therefore, the identified diagnoses may provide a decision criterion directly associated with the 2018 Classification of Periodontal and Peri-implant Diseases and Conditions to identify groups of patients who will benefit more than others, namely with less new attachment loss, from adjunctive systemic antimicrobial therapy.

In conclusion, patients with generalized stage III, grade C periodontitis obtained clinically relevant greater benefits from systemic amoxicillin/metronidazole adjunctive to SI than placebo. Clinicians treating patients similar to the population in this sub-analysis may consider the reported findings an additional decision-making aid for systemic amoxicillin/metronidazole use. Regarding generalizability, it would be interesting to investigate whether these newly identified beneficial diagnoses are suitable for other ethnicities.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to the interpretation of the data. All authors contributed to drafting and critically revising the manuscript, gave their final approval of the version to be published and agreed to be accountable for all aspects of the work. In addition Peter Eickholz, Thomas Kocher and Benjamin Ehmke conceived and designed the study. Moritz Göde, Ti-Sun Kim, Joerg Meyle, Doğan Kaner, Ulrich Schlagenhauf, Katrin Nickles, Katrin Lorenz and Inga Harks collected the data. Raphael Koch and Benjamin Ehmke supervised methodical approaches, Raphael Koch analysed data and managed the group. Peter Eickholz led the writing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not available due to data protection restrictions.

ETHICS STATEMENT

The study was approved by the Ethics Commission of the Medical Faculty of the Medical Association Westphalia-Lippe and Westphalian Wilhelm University, Münster Germany (processing number: 2006-474-f-A).

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SUPPORTING INFORMATION

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