DOI: 10.1111/prd.12440

REVIEW ARTICLE

Periodontology 2000 WILEY

Minimal invasiveness at dental implant placement: A systematic review with meta-analyses on flapless fully guided surgery

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1 | INTRODUCTION

Since the description of the biologic processes leading to implant osseointegration, clinical implant dentistry has evolved significantly. In the first stage of development, the focus was to improve the implant design and surface topography to enhance the predictability of osseointegration and, thus, to maximize the chances of implant survival.[1–3] The resulting advancements in surgical protocols and implant macro- and micro-components moved the focus to esthetic outcomes and the long-term preservation of peri-implant tissues. Therefore, during this second era of implant dentistry, relevant additional outcomes were incorporated in the broader concept of implant success.[4] Within this current notion of implant success, the concept of minimal invasiveness has attracted great attention from clinicians, manufacturers, and patients as a mean of improving the patient's experience during implant treatment, by decreasing patient morbidity and enhancing tissue preservation.

While minimal invasiveness in implantology may encompass several aspects, when related to implant placement it mainly refers to flapless procedures (ie, without elevating a mucoperiosteal flap). Indeed, flapless implant placement has been shown to reduce surgical trauma and to save time, thereby causing less patient discomfort and postoperative morbidity.[5–7] A clear hindrance of flapless surgery, however, is that the topography of the underlying bone cannot be directly visualized to guide the step-by-step bed preparation and implant placement, which may lead to implant malposition and, consequently, impairment of those outcomes describing implant success.[7] However, current breakthroughs in digital imaging technologies can overcome this barrier, as flapless surgery can now be combined with "guided implant placement".

Guided (computer-aided) surgery for implant placement was first introduced in the late 1990s and, because of those recent advancements in digital technologies, it has increasingly been used to attain a biologically and prosthetically ideal implant positioning.[8] Guided implant placement types have commonly been classified according to the level of guidance (partially vs fully) and to the capability of allowing intraoperative changes (static vs dynamic). Although recent systematic reviews have shown that static fully guided surgery has higher accuracy with respect to the planned position than free-handed and partially guided implant placement,[9] evidence synthesis is needed to verify whether this higher precision is preserved when employed flapless, and if this combination may contribute to the concept of minimal invasiveness and at the same time improve the efficacy of the implant treatment.

Therefore, the current systematic review of randomized clinical trials (RCTs) aimed to answer the following focused PICO question:

Edwin Ruales-Carrera and Sofya Sadilina contributed equally to this study.

"In adult human subjects undergoing dental implant placement (P), is minimally invasive flapless computer-aided fully guided (either dynamic or static) implant placement (I) superior to flapped conventional (FHIP or cPGIP/dPGIP) implant placement surgery (C), in terms of efficacy, patient morbidity, long-term prognosis, and costs (O)?"

2 | MATERIALS AND METHODS

This systematic review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 guidelines.[10,11] A detailed protocol was designed before the start of this study and it was registered on PROSPERO (CRD42021283366).

2.1 | Terminology: Level of guidance

Because of the heterogeneity in the terminology reported in the literature, the following definitions were employed to classify implant placement according to the level of guidance (modified from Tattan et al[9]):

- Free-handed implant placement (FHIP). Both osteotomy preparation and implant placement are performed manually, without the use of any surgical guide that may influence the course of placement into the recipient site.
- Cast-based partially guided implant placement (cPGIP). While bone bed preparation and implant placement are performed free-hand, a prosthetically driven nonrestrictive surgical guide is employed. These guides are manufactured from dental casts and have no consideration of the underlying bone morphology.
- Drill partially guided implant placement (dPGIP). The bone bed preparation is guided by means of a restrictive prosthetically driven surgical guide, manufactured considering the underlying bone morphology. Depending on their design, these guides may be used solely for the initial osteotomy (eg, pilot drill guided) or for partial or complete osteotomy. Implant placement, however, is still performed by free hand.
- Static computer-aided implant placement (sCAIP). A fully guided approach involving both restrictive osteotomy preparation and implant placement through a prosthetically driven surgical guide, fabricated based on preoperative computerized tomographic and stereolithographic data.
- Dynamic computer- aided implant placement (dCAIP). A fully guided approach of both osteotomy preparation and implant placement via the application of "a surgical navigation system that reproduces the virtual implant position directly from computerized tomographic data and allows intra-operative changes".[8]

2.2 | Terminology: Accuracy

The following five descriptions were considered as measures of implant placement accuracy:

- Biologically correct positioning. Defined dichotomously (yes/no) when the implant is placed well surrounded by native bone, at ideal distances from adjacent teeth/implants and with its head more palatal or at the level of the straight imaginary line that connects the profile of the adjacent teeth at the level of the gingival margin. This positioning has been associated with an estimated lower risk of biologic complications.[12–15]
- Prosthetically correct positioning. Defined dichotomously (yes/no) when the implant is placed according to a prosthetically driven position (the implant emerges, without applying prosthetic corrections, via the cingulum for anterior teeth or via the occlusal fossa for premolars and molars).
- Depth deviation. Metric discrepancy (measured in millimeters) between the planned and actual implant position in the vertical plane relative to the long axis of the implant body, measured from a fixed reference point (eg, most coronal or apical point of the implant body).[9]
- Angular deviation. Angular discrepancy (measured in degrees) between the planned and actual implant position respective to the center of the implant body. It is primarily ascribed to a variation in point of implant entry.[9]
- Three-dimensional bodily deviation (both coronal and apical). Metric discrepancy (measured in millimeters) between the planned and actual three-dimensional implant position, measured both in the most coronal and apical part of the implant body.[9]

2.3 | Eligibility criteria

The eligibility criteria of this systematic review were organized by the PICOS acronym.

(P) Participants. Adult human subjects (age > 18 years) needing one or more dental implants.

(I) Interventions. Flapless and computer-aided fully guided (either dynamic or static) implant placement.

(C) Comparison. Flapped and conventional (FHIP or cPGIP/dPGIP) implant placement.

(O) Outcome measures. At least one of the following outcomes of interest:

- Efficacy: implant survival, implant success, accuracy.
- Morbidity and patient satisfaction: intraoperative morbidity (complications, patient-reported outcome measures (PROMs)), postoperative morbidity (complications, PROMs, early wound healing), surgery duration, patient-perceived esthetics, and patient perception of the whole treatment.
- Long-term prognosis: marginal bone loss/levels, incidence of peri-implant diseases.
- Economic costs and entire procedural duration (including planning and realization).

(S) Studies. Only RCTs, either with parallel or split-mouth design, because no relevant carry-over or period effect could be expected for this comparison in split-mouth studies. No studies were excluded

on the basis of language, date of publication, publication status, length of follow-up, or number of included patients/arms.

2.4 | Information sources

Two review authors (MR and ER) performed in duplicate the systematic search in four electronic (Medline via PubMed, CENTRAL, Scopus, Web of Science) and gray literature (OpenGrey; www.opengrey.eu) databases, without language restrictions from outset to 4 October 2021. The complete search strategy for all electronic and gray literature databases is reported in Appendix S1.

Six implant-related key journals were also hand-searched in duplicate from 1 January 2010 to 20 October 2021 by two review authors (ER and SS): *Journal of Dental Research*, *Journal of Clinical Periodontology*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *Journal of Periodontology*, and *International Journal of Periodontics and Restorative Dentistry*. Finally, the same two reviewers also performed cross-reference checking in the bibliographies of all the included studies and of relevant review articles on the topic.[5,7,9,16–20]

All studies identified by at least one reviewer were included in the study selection phase.

2.5 | Selection process

The titles and abstracts (where available) of all the electronically identified studies were uploaded to the Rayyan website[21] (https://www.rayyan.ai/), where they were screened independently by two reviewers (ER and SS). Disagreements were resolved by discussion in joint consensus meetings with a third review author (MR), who made the final decision when resolution was not possible.

The full reports of articles potentially meeting the inclusion criteria identified during electronic screening and of publications selected through hand-searching and cross-reference checking were then evaluated independently by two review authors (MR and SS) to make the final decision. Disagreements were resolved by discussion in joint consensus meetings with a third review author (ER), who made the final decision when resolution was not possible. The reasons for excluding studies after full-text evaluation were recorded. Inter-reviewer agreement (percentage) during the screening and full-text analysis phases was calculated.

All studies meeting the inclusion criteria were included for data extraction and risk of bias assessment.

2.6 | Data extraction and management

Data from the included studies were extracted independently and in duplicate by two review authors (ER and SS) with the use of predefined data extraction forms. All the extracted data and the eventual disagreements were then jointly discussed, in the presence of a third reviewer, in consensus meetings, during which the final decisions were made. The authors from the included RCTs were contacted, asking for additional information or estimates.

For each RCT, the following data were recorded:

- General information. First author; year of publication; country.
- Methods. Study design (ie, parallel or split-mouth, clustering); setting (university, hospital, private practice); number of centers; experience of surgical operators (undergraduate students, postgraduate students or middle experienced, experts); inclusion and exclusion criteria; longest follow-up.
- Participants. Total number of randomized participants; total number of randomized implants; age (mean); gender (female, male); smoking status (nonsmokers, former smokers, smokers); edentulism type (single tooth, multiple teeth, totally edentulous arch); arch distribution (maxilla, mandible); use of antibiotic prophylaxis (yes, no); loading time (immediate/within 1 week, early/1 week-2 months, conventional/>2 months[22]).
- Interventions and comparisons. Number of study groups; for each one of the study groups: intervention (FHIP, cPGIP, dPGIP, sCAIP, dCAIP), number of allocated participants and implants, number of dropouts (participants and implants), flap elevation (flapped, flapless); implant brand; only for flapless sCAIP: static guide production (conventional, stereolithography), tissue of support of the surgical static guide (teeth-, mucosa-, bone-, pin-supported, mixed), depth control during implant placement (yes, no).
- Outcomes and results of interest. For each outcome considered in the inclusion criteria: collected (yes, no), definition, time points, mean results in each group (only for accuracy outcomes), estimates (see section 2.8 for measures of intervention effects). In any cases where the same trial reported the depth deviation outcome with more than one reference point, it was only considered once (ideally the apical one). Whenever possible, intention-to-treat data were selected.
- Study funding, and possible conflicts of interest.
- Risk of bias (see section 2.7).

In cases of multiple publications from the same trial, the data were extracted once for general characteristics (ie, general information, methods, participants, interventions, and comparisons), while the specific data (ie, outcomes and results of interest, study funding, risk of bias) were extracted from the most appropriate publications (eg, at loading and longest follow-up for implant survival in case it was reported in more than one report). In cases of multiple-arm studies also reporting study groups not fulfilling this systematic review's inclusion criteria (eg, flapped sCAIP), the results from those groups were not considered.

2.7 | Assessment of risk of bias

We assessed the risk of bias of the included trials in duplicate as part of the data extraction process, using the recommended Cochrane Risk of Bias 2 tool.[23] The risk of bias was evaluated separately for each one of the four most important outcomes (implant survival,

success, accuracy, and postoperative morbidity) in relation to the evaluation of the effect of assignment to the interventions at baseline (ie, intention-to-treat). The overall judgment of the risk of bias was made as follows[23]:

- Low risk of bias. Low risk of bias for all domains for the specific outcome.
- Some concerns. Some concerns in at least one domain regarding the specific outcome, but not a high risk of bias evaluations.
- High risk of bias. High risk of bias in at least one domain, or some concerns regarding multiple domains in a way that substantially reduces confidence in the results for the specific outcome.

2.8 | Data analysis

Depending on the nature of the variable, either the implant (eg, accuracy) or the patient (eg, surgery duration) was considered as the statistical unit. Data for continuous variables were expressed in terms of difference in means (MD) and standard error (SE), adjusted for clustering (ie, multiple implants per patient) and/or design (ie, split-mouth) whenever appropriate. When possible, MD and SEs were calculated from individual patient data (IPD) either reported in the publication[24] or provided by the authors after correspondence[25–27]; for one trial, MD and SEs were directly provided by the authors after correspondence.[28] In one RCT with a parallel-group design,[29–33] MD and SEs were calculated from crude means and standard deviations for each study group by using the appropriate formula to account for clustering, considering an intraclass correlation coefficient of .05.[9,34]

For binary variables, crude numbers were considered because of the presence of 0 events in at least one group of each possible comparison, which prevented any synthesis by means of effect measures (eg, risk ratios).

In the presence of at least two studies for each comparison, intergroup meta-analyses were carried out using the random effects method and the generic inverse variance approach. These meta-analyses were reported as MD with 95% confidence intervals (CI) and, in the presence of at least three studies, also with 95% prediction intervals.[35]

Subgroup analyses for intergroup comparisons were carried out a priori on the basis of:

- Study design (parallel, split-mouth).
- Edentulism type (single tooth, multiple teeth, totally edentulous arch).
- Tissue of support for sCAIP as intervention (tooth-supported, other).
- Risk of bias (low, some concerns/high).

Sensitivity analyses for intergroup meta-analyses were also carried out, restricting control groups to either flapped FHIP or flapped cPGIP and the intervention groups to flapless sCAIP with or without depth control.

In one study reporting a RCT with multiple treatment arms fulfilling the inclusion criteria, the most meaningful intervention and comparison group were considered for analyses.[29–33] In this study, flapless sCAIP (facilitate mucosa (Fac Mu)) and flapped FHIP were selected for the main analyses, while the other groups were selected for sensitivity analysis.

Additional planned subgroup (eg, surgical guide production, experience of surgical operators) or sensitivity (eg, restricting comparisons to dPGIP, or interventions to dCAIP) analyses for intergroup comparisons were not carried out because of lack of retrieved data.

We used intragroup meta-analyses using the random effect model when there were at least two studies assessing positioning inaccuracies of flapless sCAIP at implant level (using "effective sample sizes" for parallel studies with clustering,[34] considering an intraclass correlation coefficient = .05), or evaluating the patient-level rates of intraoperative complications of flapless sCAIP. In the case of multiple intervention arms, the flapless sCAIP (Fac Mu) group was considered.[29–33]

For intragroup meta-analyses, crude numbers were considered for binary variables (complications), while group means and standard deviations were considered for continuous variables (accuracy). Intragroup meta-analyses were reported as percentages (95% CI) for binary variables, and as means (95% CI) for continuous ones. In presence of at least three studies, 95% prediction intervals were also reported.

We assessed the interstudy heterogeneity in all meta-analyses by carefully examining the characteristics of the included studies, by inspecting the forest plots, and by calculating I^2 statistics, with values of 25%, 50%, and 75% considered as low, moderate, and high, respectively.[36]

We evaluated publication bias by visually inspecting the funnel plots since all meta-analyses included less than 10 studies, thus preventing the use of Egger's and Begg's tests.

Intergroup meta-analyses were carried out using STATA version 13.1 software (StataCorp LLC), while the intragroup ones carried out with RStudio 1.2.5033 software (RStudio); statistical significance was set in advance at P values of less than .05.

2.9 | Evaluation of certainty of evidence

One review author (MR) assessed the certainty of the body of evidence using the GRADE approach[37] as it related to those studies that provided data to the meta-analysis for each prespecified outcome considered critical or important for the comparison of the two treatment approaches. The certainty of the body of evidence was not evaluated for outcomes for which meta-analyses were not possible.

Starting from high certainty because only RCTs were included, five factors were used for downgrading (study limitations, consistency of effect, imprecision, indirectness, and publication bias), and three were used for upgrading (large effect, dose–response

gradient, and plausible confounding effect), if appropriate, the certainty of evidence. The certainty of evidence was finally considered as high, moderate, low, or very low. Methods and recommendations described in sections 8.5 and 8.7, and chapters 11 and 12, of the *Cochrane Handbook for Systematic Reviews of Interventions*, were followed.[34] GRADEpro GDT software was then used to prepare a "Summary of findings" table including an evaluation of the certainty of the body of evidence (GRADEpro GDT 2021), where all decisions to downgrade or upgrade the certainty of studies were justified using footnotes.

3 | RESULTS

3.1 | Study selection

The initial electronic database search yielded a total of 1836 entries, of which 671 were retrieved from Medline (via PubMed), 359 from CENTRAL, 180 from Scopus, 614 from Web of Science, and 12 from OpenGrey. After excluding 114 duplicates, the total number of entries was 1722. Of these, 1699 were discarded after reviewing the titles and abstracts (agreement 98.67%). Four additional articles were identified through cross-reference checking (three) and hand searching (one). In total, 27 publications were selected for full-text analysis, although 17 were excluded during this stage (the reasons for exclusion are reported in Table S1) (agreement 96.30%). A flowchart that depicts the selection process is displayed in Figure S1.

Finally, 10 publications reporting results from five RCTs and a total of 124 participants (449 implants) met the inclusion criteria and were then included in this systematic review.[24–33]

3.2 | Characteristics of the included studies

3.2.1 | Methods and participants

Table 1 depicts the methods and participants of the included studies. Three of the included trials had a split-mouth design[24,25,28] and two had a parallel design with clustering (ie, multiple implants in the same randomized participant).[26,29–33] Four RCTs were monocentric and carried out in university settings,[24,25,28–33] while the remaining one was bi-centric taking place at both a university and a private practice. Sample size varied from 10 participants (20 implants)[24,28] to 60 participants (314 implants).[29–33] Only two trials declared the inclusion of current smokers (<20% of the included participants).[26,27,29–33] Two trials only included mandibular single-tooth gaps,[25,28] one trial only single-tooth gaps but from both arches,[24] one trial only maxillary multiple adjacent missing teeth,[26,27] and the other one only maxillary and mandibular similarly distributed edentulous arches.[29–33]

Table S2 lists the inclusion and exclusion criteria reported in the included RCTs. Four trials considered as inclusion criterion the availability of enough bone without the need for bone augmentation procedures[24,25,28–33]; the other trial did not have this inclusion criterion, but reported that implants were all virtually planned embedded into bone.[26,27] All studies only included implant sites suitable for type 4 implant placement.[38] None of the included trials considered a minimum amount of keratinized tissue as inclusion criterion; however, one trial only included participants with no need for presurgical soft tissue augmentation in the implant areas.[24] A sufficient mouth opening to allow computer-aided implant placement was mentioned as inclusion criterion in only two RCTs,[25,28] while untreated periodontitis was regarded as an exclusion criteria in three trials.[24,26,27,29–33]

3.2.2 | Interventions and comparisons

Table 2 provides detailed information on the interventions and comparisons retrieved from the studies. Three trials had only two study groups (one intervention and one comparison)[24,25,28]; one trial had three study groups (one intervention and two comparisons)[26,27]; while the other trial had six study groups (four interventions and two comparisons).[29–33]

The intervention groups included flapless sCAIP in six groups of five RCTs.[24–33] In one RCT, two additional study groups included flapped sCAIP,[29–33] hence were not considered further. There were no RCTs reporting dCAIP as an intervention group.

The comparison groups included FHIP in three trials[26,28–33] and cPGIP in three trials,[24,25,29–33] in all cases including the elevation of a mucoperiosteal flap. dPGIP represented an additional comparison group in one trial[26,27]; however, because it was carried out flapless, this group was not considered further.

In summary, the current systematic review reports results from 12 treatment arms (six flapless sCAIP as intervention and six flapped FHIP/cPGIP as comparison groups) in the five included RCTs. sCAIP always used a surgical guide manufactured by stereolithography. In four arms from four RCTs[24–28] the guide was tooth-supported, while in the remaining trial it was mucosa-supported (materialize mucosa (Mat Mu) and Fac Mu).[29–33]

Guided implant insertion was carried out using a restrictive depth control system in two RCTs,[25,28] either using (Fac Mu) or not using it (Mat Mu) depending on the arm in another,[29–33] without the depth control system in another,[26,27] and unreported in the remaining one.[24]

3.3 | Efficacy, Part 1: Implant survival and implant success

The studies included in this systematic review did not consider implant success as an outcome, while only one study reported data on implant survival.[29–33] This study resulted in 100% survival because no implant was lost (evaluated up to 36 months) in either flapped FHIP, flapped cPGIP, flapless sCAIP (Mat Mu), or flapless sCAIP (Fac Mu)[29–33] (Table 3). In this study the overall risk of bias for this outcome was considered to be low (Figure 1B).

TABLE 1 Characteristics of the included studies - methods, participants, and funding

		Methods				
Reference	**Country**	**Study design**	**Setting**	**Number of centers**	**Experience of surgical operators**	**Longest follow-up**
Farley et al (2013)[24]	USA	Split-mouth	University	1	NR	Same day of implant placement
Frizzera et al (2021)[28]	Brazil	Split-mouth	University	1	Undergraduate students	1 wk
Magrin et al (2020)[25]	Brazil	Split-mouth	University	1	Expert	1 wk
Vercruyssen et al (2014a,b,c, 2015); Bernard et al (2019)[29–33]	Belgium	Parallel with clustering	University	1	Expert	3 y
Younes et al (2018, 2019)[26,27]	Belgium	Parallel with clustering	University and private practice	2	Middle experienced	12 wk

Abbreviations: N, number; NR, not reported.

[a]Actually 16 subjects (32 implants) were included, but two subjects (four implants) were excluded before randomization and two subjects (four implants) were excluded in the available "per-protocol" analyses; data about those subjects were not available.

[b]Arch distribution reported at jaw-level and not at patient-level.

[c]One additional subject was randomized, but did not receive the surgery; descriptive data about this participant were not available.

3.4 | Efficacy, Part 2: Accuracy

Accuracy outcomes were reported in four RCTs.[24–27,29–33] Prosthetically correct positioning was analyzed in one RCT,[26,27] while biologically correct positioning was never considered. Depth deviation was reported in three RCTs,[24,29–33] while angular deviation, and three-dimensional bodily deviations of the coronal and of the apical portion of the implant, were reported in four RCTs.[24–27,29–33] Figure 1C reports the risk of bias assessment for these studies. Two RCTs were considered at overall low risk of bias for these outcomes,[26,27,29–33] while one was considered to have some concerns[24] and one to have a high risk of bias, because of the exclusion of two randomized participants from the trial as a consequence of intrasurgical complications in the flapless sCAIP group (intervention-related exclusion).[25]

Table S3 reports the mean depth, angular, and three-dimensional bodily deviation values in each study group, while Table 3 reports the estimates for comparisons between groups. With regard to implant placement in a prosthetically correct position, Younes et al[26,27]

Participants (patient-level)						
Randomized—participants (implants)	Age (y)—mean	Gender—N (%)	Smoking status—N (%)	Edentulism type—N (%)	Arch distribution—N (%)	Funding and possible conflicts of interest
10 (20)	42.1	Males: 5 (50.0) Females: 5 (50.0)	Nonsmokers: 10 (100.0) Smokers: 0 (0.0)	Single tooth gap: 10 (100.0) Multiple adjacent missing teeth: 0 (0.0) Edentulous arch: 0 (0.0)	Maxilla: 3 (30.0) Mandible: 7 (70.0)	Biomet 3i
10 (20)	NR	NR	Nonsmokers: 10 (100.0) Smokers: 0 (0.0)	Single tooth gap: 10 (100.0) Multiple adjacent missing teeth: 0 (0.0) Edentulous arch: 0 (0.0)	Maxilla: 0 (0.0) Mandible: 10 (100.0)	FAESA (Faculdades Integradas Espírito-Santenses) and FAPES (Fundação de Amparo à Pesquisa e Inovação no Espírito Santo). Dérig-Implantes do Brasil provided the implants
12 (24)[a]	42	Males: 1 (8.3) Females: 11 (91.7)	NR	Single tooth gap: 12 (100.0) Multiple adjacent missing teeth: 0 (0.0) Edentulous arch: 0 (0.0)	Maxilla: 0 (0.0) Mandible: 12 (100.0)	Coordination for Improvement of Higher Education Personnel (CAPES)
60 (314)	58	Males: 29 (48.3) Females: 31 (51.7)	Nonsmokers: 53 (88.3) Smokers: 7 (11.7)	Single tooth gap: 0 (0.0) Multiple adjacent missing teeth: 0 (0.0) Edentulous arch: 60 (100.0)	Maxilla: 39 (54.2)[b] Mandible: 33 (45.8)[b]	Dentsply Sirona provided implants, prosthetic materials, and stereolithographic guides. One of the authors was employed at Dentsply Sirona at the time of the publication of Bernard et al (2019)
32 (71)[c]	57.6	Males: 11 (34.4) Females: 21 (65.6)	Nonsmokers: 26 (81.2) Smokers: 6 (18.8)	Single tooth gap: 0 (0.0) Multiple adjacent missing teeth: 32 (100.0) Edentulous arch: 0 (0.0)	Maxilla: 32 (100.0) Mandible: 0 (0.0)	Dentsply Sirona

reported that 80.8% and 100.0% of the implants could be restored with a screw-retained prosthesis in the flapped free-handed and flapless sCAIP groups, respectively.

The mean depth deviation varied from 0.43 to 1.24 mm in flapless sCAIP and from 0.50 to 2.20 mm in flapped FHIP/cPGIP groups. While statistically significantly less depth deviation was reported in flapless sCAIP compared with flapped FHIP/cPGIP in one RCT,[29–33] two other RCTs reported no statistically significant differences.[24,26,27]

The mean angular deviation varied from 2.20 to 3.68 degrees in flapless sCAIP and from 3.50 to 9.92 degrees in flapped FHIP/cPGIP groups. In three RCTs there was less angular deviation in flapless sCAIP compared with flapped FHIP/cPGIP,[25–27,29–33] while in one trial[24] there was a nonsignificant tendency in the same direction.

Mean coronal three-dimensional bodily deviation varied from 0.73 to 2.34 mm in flapless sCAIP and from 1.45 to 2.97 mm in flapped FHIP/cPGIP groups. Mean apical three-dimensional bodily deviation varied from 0.97 to 2.53 mm in flapless sCAIP vs 2.11 to 3.40 mm in flapped FHIP/cPGIP groups. Two trials reported less three-dimensional bodily deviation, both in the coronal and in the

TABLE 2 Characteristics of the included studies - interventions and comparisons

Reference	Number of study groups	Interventions and comparisons	Number allocated in each group—N participants (N implants)	Number of dropouts in each group—N participants (N implants)	Flap elevation
Farley et al (2013)[24]	2	Comparison: cPGIP	cPGIP: 10 (10)	cPGIP: 0 (0)	cPGIP: Flapped
		Intervention: sCAIP	sCAIP: 10 (10)	sCAIP: 0 (0)	sCAIP: Flapless
Frizzera et al (2021)[28]	2	Comparison: FHIP	cPGIP: 10 (10)	cPGIP: 0 (0)	cPGIP: Flapped
		Intervention: sCAIP	sCAIP: 10 (10)	sCAIP: 0 (0)	sCAIP: Flapless
Magrin et al (2020)[25]	2	Comparison: cPGIP	cPGIP: 12 (12)	cPGIP: 0 (0)	cPGIP: Flapped
		Intervention: sCAIP	sCAIP: 12 (12)	sCAIP: 0 (0)	sCAIP: Flapless
Vercruyssen et al (2014a,b,c, 2015), Bernard et al (2019)[29–33]	6	Comparison 1: FHIP	FHIP: 12 (51)	FHIP: 0 (0)	FHIP: Flapped
		Comparison 2: cPGIP	cPGIP: 12 (51)	cPGIP: 0 (0)	cPGIP: Flapped
		Intervention 1: sCAIP (Mat Mu)	sCAIP (Mat Mu): 12 (55)	sCAIP (Mat Mu): 0 (0)[b]	sCAIP (Mat Mu): Flapless
		Intervention 2: sCAIP (Fac Mu)	sCAIP (Fac Mu): 12 (52)	sCAIP (Fac Mu): 0 (0)[b]	sCAIP (Fac Mu): Flapless
		Intervention 3: sCAIP (Mat Bo)	sCAIP (Mat Bo): 12 (53)	sCAIP (Mat Bo): 0 (0)[a]	sCAIP (Mat Bo): Flapped[c]
		Intervention 4: sCAIP (Fac Bo)	sCAIP (Fac Bo): 12 (52)	sCAIP (Fac Bo): 0 (0)[b]	sCAIP (Fac Bo): Flapped[c]
Younes et al (2018, 2019)[26,27]	3	Comparison 1: FHIP	FHIP: 11 (26)	FHIP: 0 (0)	FHIP: Flapped
		Comparison 2: dPGIP	dPGIP: 11 (24)	dPGIP: 0 (0)	dPGIP: Flapless[c]
		Intervention: sCAIP	sCAIP: 10 (21)	sCAIP: 0 (0)	sCAIP: Flapless

Abbreviations: cPGIP, cast-based partially guided implant placement; dPGIP, drill partially guided implant placement; Fac, facilitate; FHIP, free-handed implant placement; Mat, materialize; Mu, mucosa-supported; N, number; NR, not reported; sCAIP, static computer-aided implant placement.

[a]Vercruyssen et al[31] had one patient (four implants) as dropout in the sCAIP (Mat Bo) group.

[b]Bernard et al[33] had one patient (four implants) as dropout in each one of the following three groups: sCAIP (Mat Mu), sCAIP (FacMu), sCAIP (Fac Bo).

[c]The results from those groups were not considered, as they did not fulfill the systematic review inclusion criteria.

apical portion of the implants with flapless sCAIP compared with flapped FHIP/cPGIP,[26,27,29–33] while the other two trials reported no statistically significant differences.[24,25]

Accuracy outcomes did not show statistically significant differences in the only trial that also compared flapless sCAIP with and without depth control.[29–33] In the same trial, more depth deviation was observed in flapped cPGIP compared with flapped FHIP (without differences in the other accuracy outcomes).[29–33]

Intragroup meta-analyses describing the accuracy errors for flapless sCAIP are reported in Figure 2.

Flapless sCAIP resulted in a mean depth deviation of 0.76 mm, an angular deviation of 2.57 mm, a coronal three-dimensional bodily deviation of 1.43 mm and an apical three-dimensional bodily deviation of 1.68, when compared with the planned position. While intragroup meta-analyses on angular deviations showed a low level of heterogeneity, the other accuracy errors showed high heterogeneity.

Intergroup meta-analyses comparing accuracy outcomes in flapless sCAIP with flapped FHIP/cPGIP are reported in Figure 3. There was statistically significantly less angular deviation (MD = −3.88 degrees) and apical three-dimensional bodily deviation (MD = −0.75 mm) in flapless sCAIP compared with flapped FHIP/cPGIP. Less depth deviation (MD = −0.28 mm) and coronal three-dimensional bodily deviation (MD = −0.60 mm) were also found in

			Only sCAIP		
Antibiotic prophylaxis	Loading time	Implant brand	Guide production	Tissue of support	Depth control during implant placement
NR	NR	Biomet 3i	Stereolithography	Tooth-supported	NR
Yes	NR	Singular Dérig-Implantes do Brasil	Stereolithography	Tooth-supported	Yes
No	NR	Neodent	Stereolithography	Tooth-supported	Yes
Yes	Conventional (>2 mo), with the exception of one participant (immediate)	Astra Tech TX (Astra Tech)	Stereolithography	Mat Mu & Fac Mu: Mucosa-supported Mat Bo & Fac Bo: Pin-supported	Mat Mu & Mat Bo: No Fac Mu & Fac Bo: Yes
Yes	Conventional (>2 mo)	OsseoSpeed EV (Astra Tech)	Stereolithography	Tooth-supported	No

flapless sCAIP vs flapped FHIP/cPGIP, although without reaching the level of statistical significance. All intergroup meta-analyses for accuracy outcomes demonstrated a moderate to high level of heterogeneity. Visual inspection of funnel plots showed no obvious evidence of publication bias.

Sensitivity analyses (Appendix S1) demonstrated the same tendencies when restricting the intervention groups to flapless sCAIP with or without depth and the control group to flapped FHIP or flapped cPGIP. However, the magnitude of the estimates was almost double in terms of angular deviation and three-dimensional bodily deviation (both coronal and apical) when restricting the intervention arms to flapless sCAIP without depth control and the control groups to flapped FHIP.

Subgroup meta-analyses (Appendix S1) revealed better accuracy in flapless sCAIP compared with flapped FHIP/cPGIP in edentulous arches or multiple adjacent teeth gaps, as well as in trials with a parallel design or with a low risk of bias. However, these subgroups always corresponded to the same two trials.[26,27,29–33]

3.5 | Postoperative morbidity

Three of the included RCTs reported data on postoperative morbidity outcomes.[24–27,29–33] The rate of postoperative complications was reported in two RCTs.[25,28] Postoperative pain was reported in three RCTs,[25,28–33] while postoperative swelling was reported in

TABLE 3 Characteristics of the included studies - outcomes and results of interest: efficacy

Reference	Implant survival (total number)	Implant success (total number)	Time-point for accuracy outcomes	Accuracy 1—Biologically correct positioning (total number)
Farley et al (2013)[24]	NC	NC	Just after surgery	NC
Frizzera et al (2021)[28]	NC	NC	NC	NC
Magrin et al (2020)[25]	NC	NC	1 wk	NC
Vercruyssen et al (2014a,b,c, 2015), Bernard et al (2019)[29–33]	*Implant survival at loading (4 mo)* FHIP: 51 out of 51 implants (12 out of 12 participants). cPGIP: 51 out of 51 implants (12 out of 12 participants). sCAIP (Mat Mu): 55 out of 55 implants (12 out of 12 participants). sCAIP (Fac Mu): 52 out of 52 implants (12 out of 12 participants). *Implant survival at 36 mo* FHIP: 51 out of 51 implants (12 out of 12 participants). cPGIP: 51 out of 51 implants (12 out of 12 participants). sCAIP (Mat Mu): 51 out of 51 implants (11 out of 11 participants). sCAIP (Fac Mu): 48 out of 48 implants (11 out of 11 participants)	NC	10 d	NC
Younes et al (2018, 2019)[26,27]	NC	NC	At implant loading (12 wk)	NC

Note: Time points consider implant placement as reference. Results on binary outcomes are reported as crude numbers, while results on continuous outcomes are reported as MD (SE).

Abbreviations: Bo, bone-supported; cPGIP, cast-based partially guided implant placement; dPGIP, drill partially guided implant placement; Fac, Facilitate; FHIP, free-handed implant placement; Mat, Materialise; MD, difference in means; mm, millimeters; Mu, mucosa-supported; NC, not collected; NR, not reported; sCAIP, static computer-aided implant placement; SE, standard error.

[a]Apical.

[b]Coronal.

[c]Defined as implants that could be restored with screw-retained restoration.

*$P < .05$.

two[25,29–33]; in one study, these outcomes were also assessed indirectly by counting the number of analgesics and anti-inflammatory drugs.[28] Bleeding,[25] ecchymosis,[25] and oral health-related quality of life (OHRQol) were also reported in one study each.[29–33] Wound healing as an outcome was not reported in any study.

Figure 1D reports the risk of bias assessment in relation to these outcomes. Two studies were considered to have some concerns, in relation to either missing outcome data[25] or selection or measurement bias,[28] while one trial was considered to have an overall low risk of bias.[29–33]

Table 4 reports the between-group estimates for postoperative morbidity. In two studies there were no postoperative complications in both the flapless sCAIP and flapped cPGIP groups.[25,28] In one study, statistically significantly less postoperative pain was reported for flapless sCAIP compared with flapped FHIP/cPGIP,[29–33] while in the remaining two RCTs[25,28] there was only a nonsignificant tendency for less pain in flapless sCAIP compared with flapped cPGIP. Similarly, in one study there was a nonsignificant tendency for using fewer analgesics and anti-inflammatory drugs in the first 7 postoperative days,[28] and in another less postoperative bleeding, swelling, and ecchymosis[25] in flapless sCAIP compared with flapped cPGIP. The trial conducted by Vercruyssen et al and Bernard et al[29–33] reported less postoperative swelling only in the flapless sCAIP group (Fac Mu) vs flapped

Accuracy 2—Prosthetically correct positioning (total number)	Accuracy 3—Depth deviation (mm)	Accuracy 4—Angular deviation (degrees)	Accuracy 5—3D bodily deviations (coronal) (mm)	Accuracy 6—3D bodily deviations (apical) (mm)
NC	sCAIP vs cPGIP[a]: MD = −0.35 (SE = 0.32)	sCAIP vs cPGIP: MD = −2.45 (SE = 1.38)	sCAIP vs cPGIP: MD = −0.53 (SE = 0.34)	sCAIP vs cPGIP. MD = −0.72 (SE = 0.40)
NC	NC	NC	NC	NC
NC	NC	sCAIP vs cPGIP: MD = −1.30 (SE = 0.54)*	sCAIP vs cPGIP: MD = 0.41 (SE = 0.36)	sCAIP vs cPGIP: MD = 0.34 (SE = 0.39)
NC	cPGIP vs FHIP[b]: MD = 0.95 (SE = 0.27)* sCAIP (Mat Mu) vs FHIP[b]: MD = −0.51 (SE = 0.17)* sCAIP (Fac Mu) vs FHIP[b]: MD = −0.51 (SE = 0.18)* sCAIP (Mat Mu) vs cPGIP[b]: MD = −1.46 (SE = 0.23)* sCAIP (Fac Mu) vs cPGIP[b]: MD = −1.46 (SE = 0.24)* sCAIP (Fac Mu) vs sCAIP (Mat Mu)[b]: MD = 0.00 (SE = 0.13)	cPGIP vs FHIP: MD = −1.49 (SE = 1.22) sCAIP (Mat Mu) vs FHIP: MD = −7.06 (SE = 0.93)* sCAIP (Fac Mu) vs FHIP: MD = −7.21 (SE = 0.94)* sCAIP (Mat Mu) vs cPGIP: MD = −5.57 (SE = 0.80)* sCAIP (Fac Mu) vs cPGIP: MD = −5.72 (SE = 0.81)* sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = −0.15 (SE = 0.32)	cPGIP vs FHIP: MD = 0.20 (SE = 0.32) sCAIP (Mat Mu) vs FHIP: MD = −1.54 (SE = 0.25)* sCAIP (Fac Mu) vs FHIP: MD = −1.39 (SE = 0.26)* sCAIP (Mat Mu) vs cPGIP: MD = −1.74 (SE = 0.23)* sCAIP (Fac Mu) vs cPGIP: MD = −1.59 (SE = 0.24)* sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = 0.15 (SE = 0.13)	cPGIP vs FHIP: MD = 0.49 (SE = 0.35) sCAIP (Mat Mu) vs FHIP: MD = −1.34 (SE = 0.25)* sCAIP (Fac Mu) vs FHIP: MD = −1.31 (SE = 0.26)* sCAIP (Mat Mu) vs cPGIP: MD = −1.83 (SE = 0.27)* sCAIP (Fac Mu) vs cPGIP: MD = −1.80 (SE = 0.28)* sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = 0.03 (SE = 0.15)
FHIP: 21 out of 26 implants (NR out of 11 participants)[c] sCAIP: 21 out of 21 implants (10 out of 10 participants)[c]	sCAIP vs FHIP[a]: MD = −0.08 (SE = 0.12)	sCAIP vs FHIP: MD = −4.68 (SE = 1.36)*	sCAIP vs FHIP: MD = −0.72 (SE = 0.15)*	sCAIP vs FHIP: MD = −1.13 (SE = 0.29)*

FHIP group. In the same trial, higher values for of OHRQol (ie, less postoperative discomfort and inconvenience in daily life[39]) were reported for flapless sCAIP (Mat Mu), but not for flapless sCAIP (Fac Mu), compared with flapped FHIP/cPGIP.[29–33]

The only trial comparing cPGIP with FHIP reported greater postoperative pain and higher values of OHRQol in flapped FHIP compared with flapped cPGIP, but no differences in postoperative swelling.[29–33] The same trial also reported no statistically significant differences in postoperative morbidity when comparing flapless sCAIP with and without depth control (ie, Fac Mu vs Mat Mu).[29–33]

Intergroup meta-analyses (flapless sCAIP vs flapped FHIP/cPGIP) on postoperative morbidity outcomes from at least two included trials are reported in Figure 4. They indicate statistically significantly less postoperative pain (MD = −17.09 mm on the VAS) and a nonstatistically significant tendency for less postoperative swelling (MD = −6.59 mm on the VAS) in flapless sCAIP compared with flapped FHIP/cPGIP, in both cases with a high level of heterogeneity. Visual inspection of funnel plots showed no obvious evidence of publication bias.

Sensitivity analyses (Appendix S1) showed the same tendency when restricting control groups to either flapped FHIP or flapped

FIGURE 1 Risk of bias summary of the included studies: review of authors' judgments in relation to the four outcomes considered critical or important for the comparison of the two treatment approaches: A, Implant survival; B, Implant success; C, Accuracy; and D, Postoperative morbidity

cPGIP, as well as when restricting intervention groups to flapless sCAIP with depth control.

Subgroup meta-analyses (Appendix S1) were only possible for postoperative pain, revealing results that were consistent with the main analyses when only considering the two split-mouth trials employing tooth-supported guides and including single-tooth gaps.[25,28]

3.6 | Additional PROMs and intraoperative outcomes

Surgery duration was measured in three trials,[26,28–33] while the rate of intraoperative complications was reported in three trials[25–28] and two trials each analyzed intraoperative pain[25,29–33] and discomfort.[25,28] Patients' perception of the overall treatment was reported in only one trial,[28] while no trial reported on patient self-perceived esthetics.

Table 5 reports the estimates for comparisons between groups with respect to these outcomes. The reporting of intraoperative complications was 0% for flapped cPGIP,[25,28] while it ranged from 0%[28] to 30%[26,27] for flapless sCAIP. These included nonfitting guides,[26,27] surgical guide not delivered in time,[26,27] fracture of the insertion driver inside the implant,[25] and perforation of buccal bone.[25]

Less intraoperative pain was reported in one trial for flapless sCAIP (Mat Mu) than flapped FHIP/cPGIP,[29–33] while another study reported only a nonsignificant tendency.[25] The research by Vercruyssen et al and Bernard et al[29–33] also reported how these results were not applied for flapless sCAIP (Fac Mu), which was associated with more intraoperative pain than sCAIP (Mat Mu)[29–33]; no differences in intraoperative pain were reported for flapped cPGIP and flapped FHIP in the same trial.

A nonstatistically significant tendency for less intraoperative discomfort in flapless sCAIP vs flapped cPGIP was reported in the two trials reporting this outcome.[25,28]

One RCT reported a shorter surgery duration for flapless sCAIP (both Mat Mu and Fac Mu) compared with flapped FHIP, for flapless sCAIP (Mat Mu) vs flapped cPGIP, for flapped cPGIP

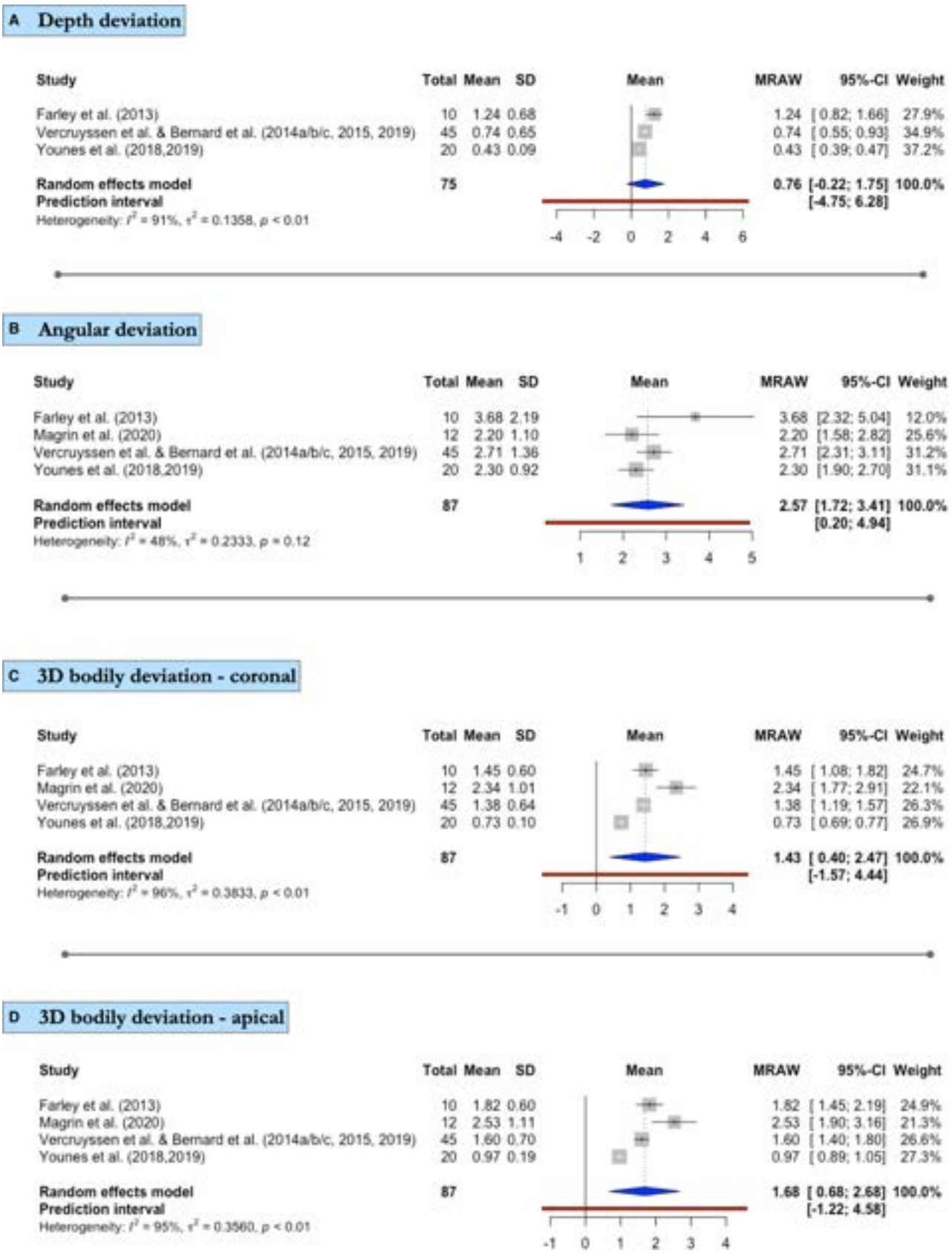

FIGURE 2 Intragroup meta-analyses. Flapless static computer-aided implant placement: accuracy outcomes. A, Depth deviation; B, Angular deviation; C, Three-dimensional bodily deviation—coronal; D, Three-dimensional bodily deviation—apical. "Effective sample sizes" were calculated for the Vercruyssen et al[29–33] (45 instead of 52) and Younes et al[26,27] (20 instead of 21) trials to account for clustering. MRAW, raw mean

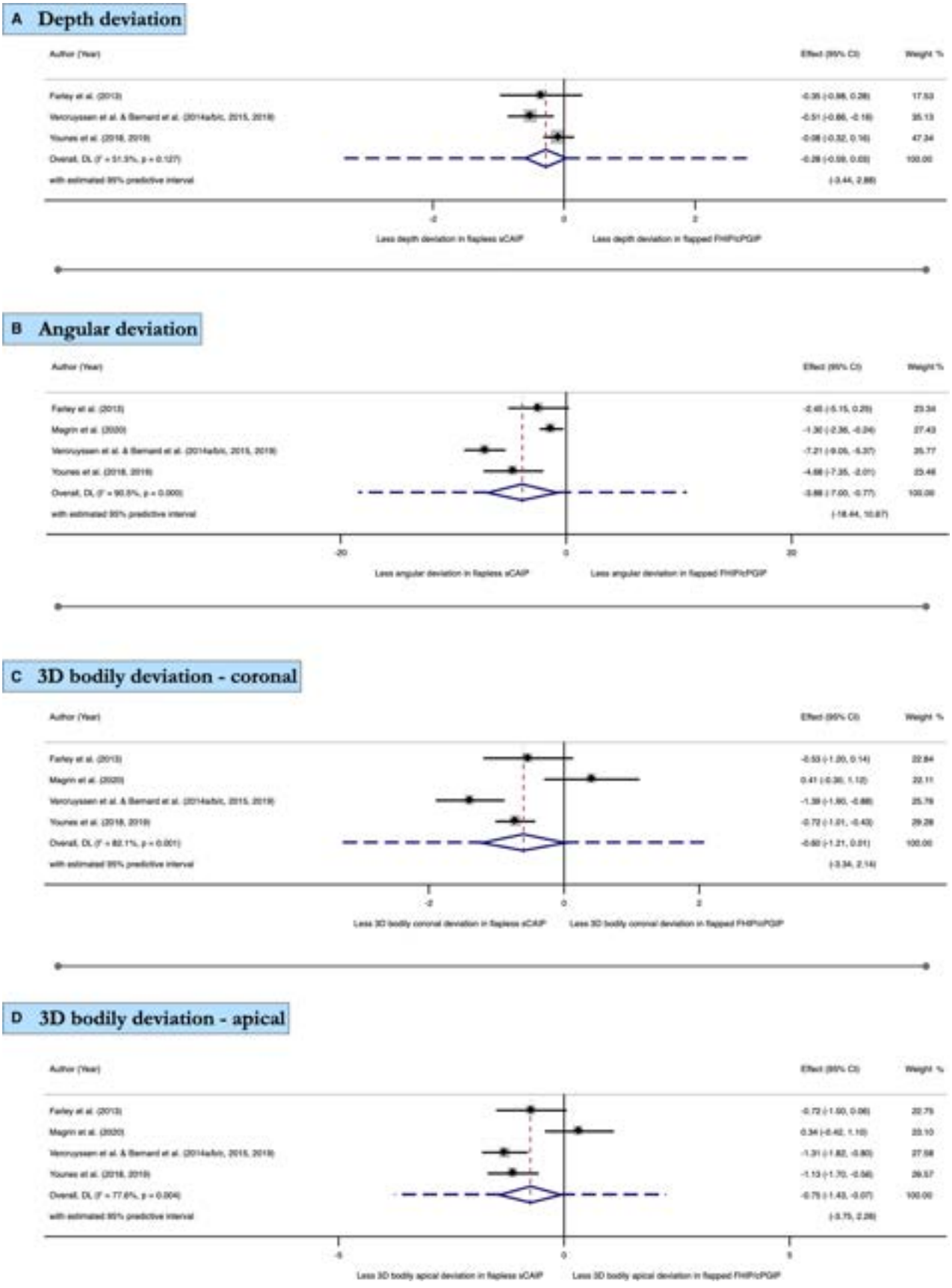

FIGURE 3 Intergroup meta-analyses. Flapped free-handed implant placement (FHIP)/cast-based partially guided implant placement (cPGIP) vs flapless static computer-aided implant placement (sCAIP): accuracy outcomes. A, Depth deviation; B, Angular deviation; C, Three-dimensional bodily deviation—coronal; D, Three-dimensional bodily deviation—apical. DL, DerSimonian-Laird

TABLE 4 Characteristics of the included studies - outcomes and results of interest: postoperative morbidity

Reference	Time point for postoperative morbidity assessment	Postoperative complications (total number)	Postoperative PROMs 1—pain[a] (mm)	Postoperative PROMs 2—number painkillers and anti-inflammatory drugs (total number)	Postoperative PROMs 3—bleeding[a] (mm)	Postoperative PROMs 4—swelling[a] (mm)	Postoperative PROMs 5—ecchymosis[a] (mm)	Postoperative PROMs 6—OHRQoL	Early wound healing
Farley et al (2013)[24]	NC	NC	NC	NC	NC	NC	NC	NC	NC
Frizzera et al (2021)[28]	Day 7[b]	cPGIP: 0 out of 10 sCAIP: 0 out of 10	sCAIP vs cPGIP: MD = −34.40 (SE = 6.20)	sCAIP vs cPGIP[c]: MD = −2.40 (SE = 0.91)	NC	NC	NC	NC	NC
Magrin et al (2020)[25]	Day 7[b]	cPGIP: 0 out of 12 sCAIP: 0 out of 12	sCAIP vs cPGIP: MD = −10.70 (SE = 6.92)	NC	sCAIP vs cPGIP: MD = −9.22 (SE = 6.85)	sCAIP vs cPGIP: MD = −14.50 (SE = 6.09)*	sCAIP vs cPGIP: MD = −7.20 (SE = 5.36)	NC	NC
Vercruyssen et al (2014a,b,c, 2015), Bernard et al (2019)[29–33]	Day 7[d]	NC	cPGIP vs FHIP: MD = −3.80 (SE = 2.00)* sCAIP (Mat Mu) vs FHIP: MD = −6.60 (SE = 1.99)* sCAIP (Fac Mu) vs FHIP: MD = −7.70 (SE = 1.88)* sCAIP (Mat Mu) vs cPGIP: MD = −2.80 (SE = 1.31)* sCAIP (Fac Mu) vs cPGIP: MD = −3.90 (SE = 1.10)* sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = −1.10 (SE = 1.16)	NC	NC	cPGIP vs FHIP: MD = −0.20 (SE = 0.81) sCAIP (Mat Mu) vs FHIP: MD = −0.60 (SE = 1.08) sCAIP (Fac Mu) vs FHIP: MD = −1.50 (SE = 0.68)* sCAIP (Mat Mu) vs cPGIP: MD = −0.40 (SE = 1.29) sCAIP (Fac Mu) vs cPGIP: MD = −1.30 (SE = 0.99) sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = −0.90 (SE = 1.20)	NC	cPGIP vs FHIP[e]: MD = −3.90 (SE = 1.09)* sCAIP (Mat Mu) vs FHIP[e]: MD = −5.10 (SE = 1.27)* sCAIP (Fac Mu) vs FHIP[e]: MD = −2.90 (SE = 1.76) sCAIP (Mat Mu) vs cPGIP[e]: MD = −2.10 (SE = 0.85)* sCAIP (Fac Mu) vs cPGIP[e]: MD = 1.00 (SE = 1.47) sCAIP (Fac Mu) vs sCAIP (Mat Mu)[e]: MD = 3.10 (SE = 1.59)	NC
Younes et al (2018, 2019)[26,27]	NC	NC	NC	NC	NC	NC	NC	NC	NC

Note: Time points consider implant placement as reference. Results on binary outcomes are reported as crude numbers, while results on continuous outcomes are reported as MD (SE).

Abbreviations: Bo, bone-supported; cPGIP, cast-based partially guided implant placement; dPGIP, drill partially guided implant placement; Fac, Facilitate; FHIP, free-handed implant placement; Mat, Materialise; MD, difference in means; mm, millimeters; Mu, mucosa-supported; NC, not collected; OHRQol, oral health-related quality of life; PROMs, patient-reported outcome measures; sCAIP, static computer-aided implant placement; SE, standard error; VAS, visual analogue scale.

[a]Self-reported VAS, measured in mm.

[b]Refers to the entire postoperative period up to day 7.

[c]Self-reported number of painkillers and anti-inflammatory drugs, recalled by the patients at the 7-d follow-up.

[d]Refers to the moment of filling the questionnaire at day 7.

[e]Self-reported answers to 15 questions about OHRQol (ranging from 0 to 75; Shugars et al[39]), with higher scores indicative of more postoperative discomfort and inconvenience in daily life.

*$P < .05$.

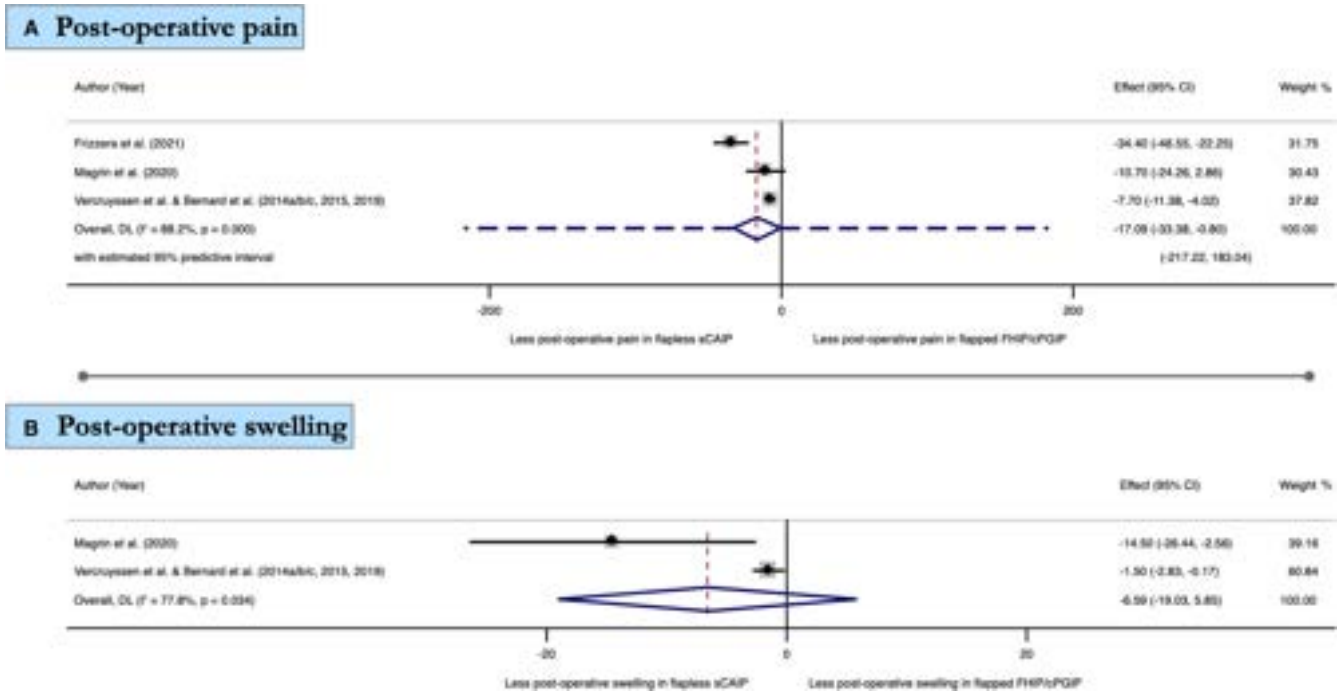

FIGURE 4 Intergroup meta-analyses. Flapped free-handed implant placement (FHIP)/cast-based partially guided implant placement (cPGIP) vs flapless static computer-aided implant placement (sCAIP): postoperative morbidity outcomes. A, Postoperative pain; B, Postoperative swelling

compared with flapped FHIP, and for flapless sCAIP (Mat Mu) vs flapless sCAIP (Fac Mu).[29–33] In the other two trials, a nonsignificant difference in surgery duration (around 20 minutes less in flapless sCAIP compared with either flapped FHIP[26,27] or flapped cPGIP[28]), was reported.

Finally, Frizzera et al[28] reported no statistically significant differences in patients' general satisfaction regarding the entire treatment when comparing flapless sCAIP with flapped cPGIP.

Intragroup meta-analyses on the rate of complications in flapless sCAIP are reported in Figure 5, resulting in a 12% overall intraoperative complications rate (moderate heterogeneity) and, consequently, an inability to place the implant with this protocol in 7% of cases (no heterogeneity).

Intergroup meta-analyses (flapless sCAIP vs flapped FHIP/cPGIP) of intraoperative PROMs and surgery duration are reported in Figure 6, indicating with no/low level of heterogeneity less intraoperative discomfort (MD = −9.36 mm of VAS) and shorter surgery duration (MD = −24.28 minutes) for flapless sCAIP compared with flapped FHIP/cPGIP. Conversely, intraoperative pain did not show statistically significant differences between groups. Visual inspection of funnel plots showed no obvious evidence of publication bias.

Sensitivity analyses (Appendix S1) showed that results were consistent with the main analyses when restricting the intervention groups to flapless sCAIP either with or without depth control, and the control groups to either flapped FHIP or flapped cPGIP.

Subgroup meta-analyses were not possible for intraoperative pain (the two trials belonged to different subgroups), while they corresponded with the main analyses for intraoperative discomfort (as both trials employed tooth-supported guides, included single-tooth gaps, and had a split-mouth design). Subgroup meta-analyses for surgery duration (Appendix S1) revealed a tendency for similar results to the main analyses when considering only studies that included single-tooth gaps or had a parallel design.

3.7 | Long-term prognosis

Despite the relevance of long-term prognosis outcomes when comparing flapless sCAIP with flapped FHIP/cPGIP, only one trial[29–33] reported a follow-up amenable for comparing changes in marginal bone levels and the incidence of peri-implant diseases between groups (Table 6).[29–33]

Marginal bone level was higher (ie, bone more apical with respect to a fixed reference point[40]) in flapped cPGIP compared with both flapped FHIP and flapless sCAIP (Mat Mu) at implant loading, 12-, and 36-month follow-ups. Flapless sCAIP (Fac Mu) showed a higher bone level than flapless sCAIP (Mat Mu) at the 36-month follow-up.[29–33]

Because of the paucity of data found, intergroup meta-analyses were not possible for these outcomes.

3.8 | Economic costs and entire procedural duration

Only the trial from Younes et al[26,27] analyzed the economic costs (up to restoration delivery), which were higher in flapless sCAIP compared with flapped FHIP, while the entire procedural duration

TABLE 5 Characteristics of the included studies - outcomes and results of interest: intraoperative outcomes and additional PROMs

	Intraoperative outcomes					Additional PROMs		
Reference	Intraoperative complications (total number)	Time point for intraoperative PROMs assessment	Intraoperative PROMs 1—pain[a] (mm)	Intraoperative PROMs 2—discomfort[a] (mm)	Surgery duration (min)	Time point for additional PROMs assessment	Patient self-perceived esthetics	Patient perception of the whole treatment (mm)
Farley et al (2013)[24]	NC	NC	NC	NC	NC	NC	NC	NC
Frizzera et al (2021)[28]	cPGIP: 0 out of 10 sCAIP: 0 out of 10	Just after surgery	NC	sCAIP vs cPGIP: MD = −11.00 (SE = 5.30)	sCAIP vs cPGIP: MD = −26.77 (SE = 2.83)	NR	NC	sCAIP vs cPGIP[b]: MD = 0.50 (SE = 0.20)
Magrin et al (2020)[25]	cPGIP: 0 out of 14 sCAIP: 2 out of 14[c]	Day 7, answering in relation to the day of surgery	sCAIP vs cPGIP: MD = −13.40 (SE = 10.05)	sCAIP vs cPGIP: MD = −7.30 (SE = 5.93)	NC	NC	NC	NC
Vercruyssen et al (2014a,b,c, 2015), Bernard et al (2019)[29–33]	NC	Just after surgery	cPGIP vs FHIP: MD = 1.30 (SE = 5.22) sCAIP (Mat Mu) vs FHIP: MD = −10.50 (SE = 4.25)* sCAIP (Fac Mu) vs FHIP: MD = 0.80 (SE = 5.42) sCAIP (Mat Mu) vs cPGIP: MD = −11.80 (SE = 3.96)* sCAIP (Fac Mu) vs cPGIP: MD = −0.50 (SE = 5.19) sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = 11.30 (SE = 4.24)*	NC	cPGIP vs FHIP: MD = −23.60 (SE = 3.52)* sCAIP (Mat Mu) vs FHIP. MD = −28.50 (SE = 3.35)* sCAIP (Fac Mu) vs FHIP. MD = −22.00 (SE = 3.78)* sCAIP (Mat Mu) vs cPGIP: MD = −4.90 (SE = 2.42)* sCAIP (Fac Mu) vs cPGIP: MD = 1.60 (SE = 2.94) sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = 6.50 (SE = 2.79)*	NC	NC	NC
Younes et al (2018, 2019)[26,27]	FHIP: NR sCAIP: NR out of 21 implants (3 out of 10 participants)[d]	NC	NC	NC	sCAIP vs FHIP: MD = −17.54 (SE = 6.99)	NC	NC	NC

Note: Time points consider implant placement as reference. Results on binary outcomes are reported as crude numbers, while results on continuous outcomes are reported as MD (SE).

Abbreviations: Bo, bone-supported; cPGIP, cast-based partially guided implant placement; dPGIP, drill partially guided implant placement; Fac, Facilitate; FHIP, free-handed implant placement; Mat, Materialise; MD, difference in means; mm, millimeters; Mu, mucosa-supported; NC, not collected; NR, not reported; PROMs, patient-reported outcome measures; sCAIP, static computer-aided implant placement; SE, standard error; VAS, visual analogue scale.

[a]Self-reported VAS, measured in mm.

[b]Self-reported "general satisfaction" on a VAS, measured in mm.

[c]Complications reported: "(a) fracture of the buccal bone wall during implant insertion, which hampered the implant placement at the planned site (one implant); (b) fracture of the insertion driver inside the implant during its installation, preventing the implant from reaching the position indicated in the planning (one implant)."

[d]Refers to nonfitting surgical guide which was solved before surgery (two participants, four implants), or surgical guide not delivered in time (with consequent FHIP, but retained in sCAIP group for intention-to treat analysis).

*$P < .05$.

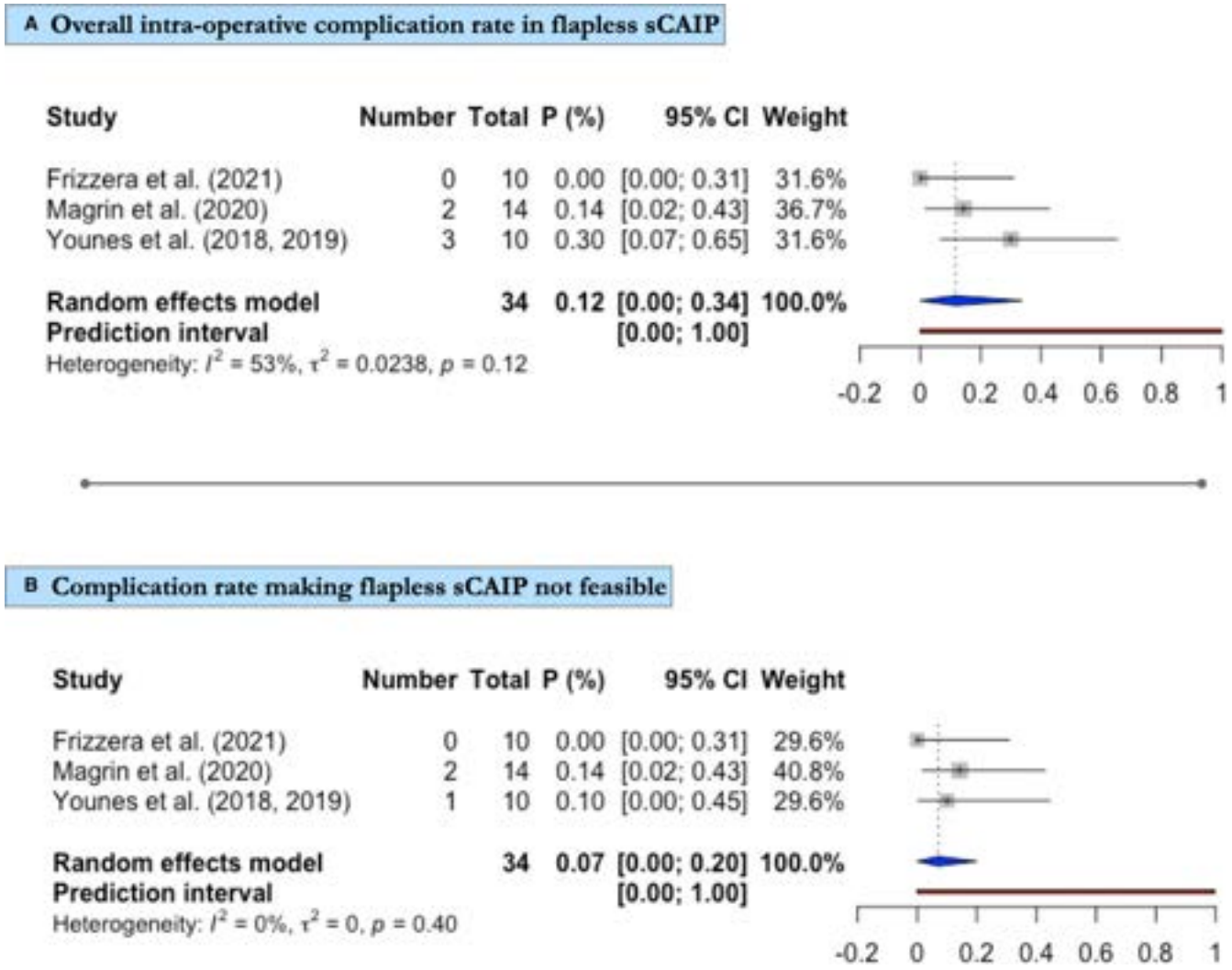

FIGURE 5 Intragroup meta-analyses. Flapless static computer-aided implant placement (sCAIP): intraoperative complications. A, Overall intraoperative complication rate; B, Complication rate making flapless sCAIP infeasible. DL, DerSimonian-Laird.

(planning + surgery) did not differ between the groups (Table 6). Data on long-term costs were not reported.

Because of the paucity of data found, intergroup meta-analyses were not possible for these outcomes.

3.9 | Certainty of evidence

The "summary of findings" is reported in Table 7. Certainty of evidence was not evaluated for some of the outcomes considered as critical or important (ie, implant survival and success, biologically and prosthetically correct positioning), as evidence for those outcomes was absent or based on single RCTs. The certainty of the body of evidence was considered high for reduction in angular deviation, moderate for reductions in depth and apical three-dimensional bodily deviations, low for reductions in coronal three-dimensional bodily deviation and postoperative pain, and very low for reduction in postoperative swelling, in flapless sCAIP vs flapped FHIP/cPGIP.

4 | DISCUSSION

Results from the current systematic review indicate that flapless sCAIP is more accurate than flapped FHIP/cPGIP with respect to the planned position, especially in terms of angular deviation (4 degrees less deviation) and apical three-dimensional bodily deviations (0.75 mm less deviation). This difference in accuracy was even higher when comparing only with flapped FHIP. However, evidence regarding more clinically relevant outcomes of efficacy (implant survival and success, prosthetically and biologically correct positioning), is currently lacking. Furthermore, flapless sCAIP, when compared with flapped FHIP/cPGIP surgeries, have a shorter duration (~24 minutes less) and appear to result in less intraoperative and postoperative morbidity. However, at patient level, a 12% group-specific intraoperative complication rate was reported for flapless sCAIP, which finally made it infeasible in 7% of cases. Evidence from single RCTs indicates higher economic costs in flaples sCAIP and similar entire procedural duration (ie, including planning) between groups, while inconclusive to no evidence was found with regard to long-term

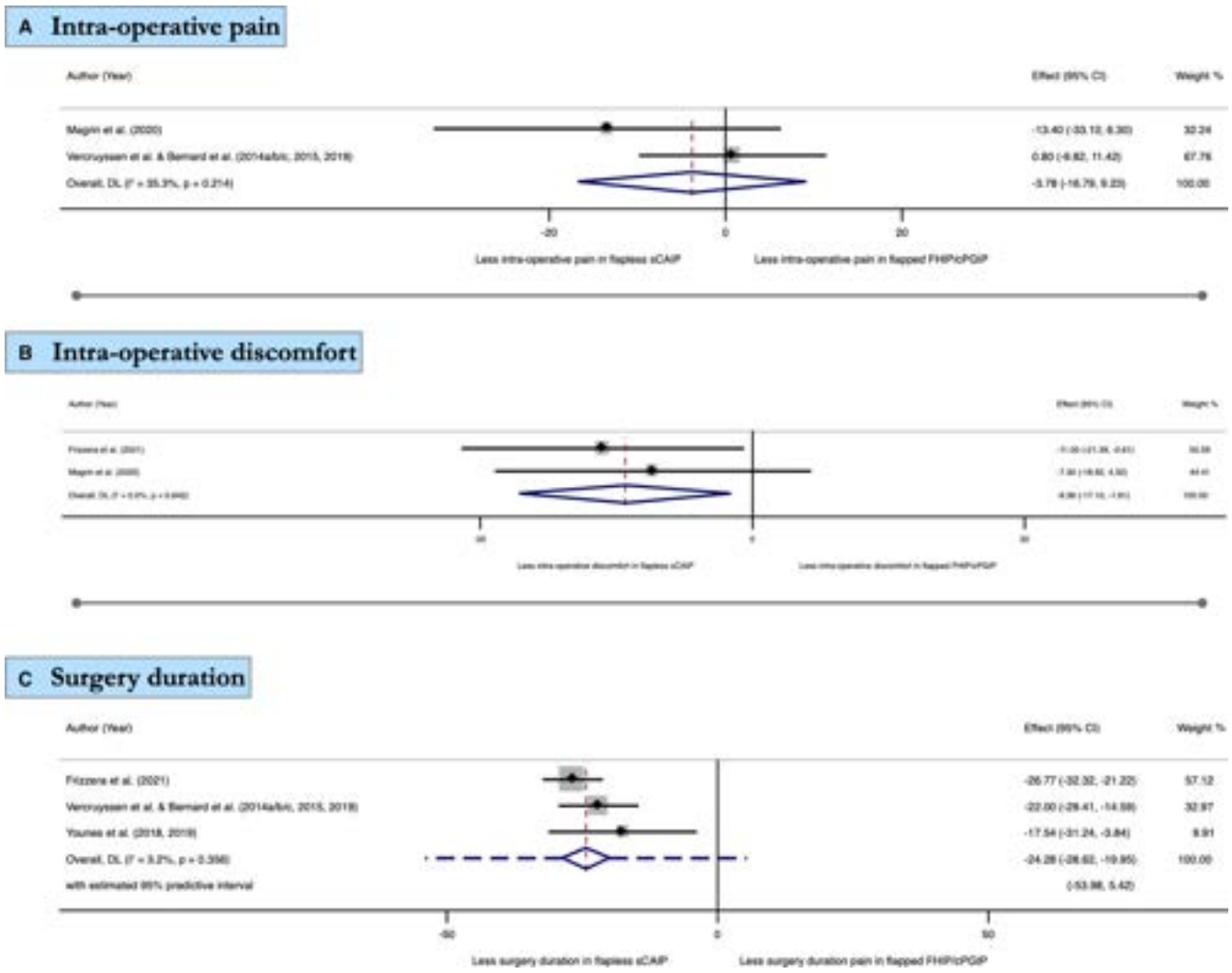

FIGURE 6 Intergroup meta-analyses. Flapped free-handed implant placement (FHIP)/cast-based partially guided implant placement (cPGIP) vs flapless static computer-aided implant placement (sCAIP): intraoperative PROMs and surgery duration. A, Intraoperative pain; B, Intraoperative discomfort; C, Surgery duration. DL, DerSimonian-Laird.

prognosis outcomes (ie, changes in marginal bone levels and incidence of peri-implant diseases). In summary, the findings from the current systematic review corroborate the reduced invasiveness of flapless implant placement combined with the accuracy of guided surgery (flapless sCAIP). However, there were no RCTs evaluating dCAIP, which limits the applicability of the present findings to flapless sCAIP.

The reduced invasiveness of flapless surgery was already indicated in RCTs from the beginning of the 21st century. Fortin et al[6] showed less postoperative pain measured on VAS and less consumption of analgesic medications in a RCT comparing flapless with flapped surgery. Similarly, the results from the split-mouth RCT conducted by Cannizzaro et al[41] showed shorter surgery (a difference of 17 minutes) duration and less postoperative swelling in fully edentulous cases treated with flapless compared with flapped surgery. The difference in the magnitude of duration compared with the results from this systematic review (~24 minutes) may indirectly suggest that computer guidance (sCAIP) may provide an additional reduction in surgery duration to the one provided by flapless surgery alone.

The higher accuracy of sCAIP compared with FHIP/cPGIP with respect to the planned position, regardless of the elevation (or not) of a mucoperiosteal flap, was already indicated in a recent systematic review, which reported lower meta-analytical estimates for angular, coronal, and apical deviation in fully guided surgery of a similar magnitude to that found in the current study.[9] Raico Gallardo et al[18] reported that the tissue of support of the guide may have an influence on accuracy outcomes, but this concept could not be verified in the current systematic review, as four out of the five included trials employed tooth-supported guides. Finally, despite being more accurate than flapped FHIP/cPGIP with respect to the planned position, results from the current systematic review suggest that flapless sCAIP is not free from positioning errors. Inaccuracies of a similar magnitude were already reported in the systematic review by Tahamaseb et al[19] studying the accuracy of sCAIP irrespective of flap elevation

TABLE 6 Characteristics of the included studies - outcomes and results of interest: long-term prognosis, economic costs, and entire procedural duration

Reference	Long-term prognosis		Economic costs (Euros)	Whole procedural duration[a] (min)
	Marginal bone loss/level (mm)	Peri-implant diseases incidence (total number)		
Farley et al (2013)[24]	NC	NC	NC	NC
Frizzera et al (2021)[28]	NC	NC	NC	NC
Magrin et al (2020)[25]	NC	NC	NC	NC
Vercruyssen et al (2014a,b,c, 2015), Bernard et al (2019)[29–33]	*At implant loading (4 mo)*[b] cPGIP vs FHIP: MD = 0.56 (SE = 0.16)* sCAIP (Mat Mu) vs FHIP: MD = 0.23 (SE = 0.12) sCAIP (Fac Mu) vs FHIP: MD = 0.19 (SE = 0.15) sCAIP (Mat Mu) vs cPGIP: MD = −0.44 (SE = 0.16)* sCAIP (Fac Mu) vs cPGIP: MD = −0.37 (SE = 0.19) sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = 0.07 (SE = 0.16) *12-mo*[b] cPGIP vs FHIP: MD = 0.55 (SE = 0.18)* sCAIP (Mat Mu) vs FHIP: MD = 0.14 (SE = 0.11) sCAIP (Fac Mu) vs FHIP: MD = 0.25 (SE = 0.17) sCAIP (Mat Mu) vs cPGIP: MD = −0.41 (SE = 0.19)* sCAIP (Fac Mu) vs cPGIP: MD = −0.30 (SE = 0.23) sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = 0.11 (SE = 0.18) *36 mo*[b] cPGIP vs FHIP: MD = 0.30 (SE = 0.13)* sCAIP (Mat Mu) vs FHIP: MD = −0.10 (SE = 0.10) sCAIP (Fac Mu) vs FHIP: MD = 0.40 (SE = 0.22) sCAIP (Mat Mu) vs cPGIP: MD = −0.40 (SE = 0.12)* sCAIP (Fac Mu) vs cPGIP: MD = 0.10 (SE = 0.23) sCAIP (Fac Mu) vs sCAIP (Mat Mu): MD = 0.50 (SE = 0.21)*	NR. The authors reported that three patients were diagnosed as affected by peri-implantitis at the 12-mo follow-up according to the Sanz and Chapple (2012) case definition,[42] without indicating their study groups	NC	NC
Younes et al (2018, 2019)[26,27]	NC	NC	sCAIP vs FHIP[c]: MD = 222.52 (SE = 7.40)*	sCAIP vs FHIP: MD = 2.86 (SE = 7.26)

Note: Time points consider implant placement as reference. Results on continuous outcomes are reported as MD (SE).

Abbreviations: Bo, bone-supported; cPGIP, cast-based partially guided implant placement; dPGIP, drill partially guided implant placement; Fac, Facilitate; FHIP, free-handed implant placement; Mat, Materialise; MD, difference in means; mm, millimeters; Mu, mucosa-supported; NC, not collected; NR, not reported; sCAIP, static computer-aided implant placement; SE, standard error.

[a]The time necessary for the whole implant placement procedure (planning and surgery).

[b]Refers to bone levels.[40]

[c]The estimated imposed costs to the patient were calculated simulating that treatments were performed in normal clinical practice. A distinction was made between standard costs (including radiographic examinations and prosthetic fees), which were identical for the study groups, and additional costs, which were group-specific for sCAIP groups; evaluated at 12 wk (restoration delivery).

*$P < .05$.

TABLE 7 Summary of findings

Authors: **Mario Romandini, Edwin Ruales, Sofya Sadilina, Christoph Hämmerle, Mariano Sanz**											
Question: **Flapless sCAIP compared with flapped FHIP/cPGIP for implant placement**											
Setting: **When the objective is to guarantee minimally invasiveness**											
Certainty assessment							**No. of implants**		**Effect**		
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**flapless sCAIP**	**flapped FHIP/ cPGIP**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Depth deviation (assessed with: Metric discrepancy [measured in mm] on CBCT)												
3	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	83	87	—	MD **0.28 mm lower** (0.59 lower to 0.03 higher)	⨁⨁⨁◯ Moderate	Important
Angular deviation (assessed with: Angular discrepancy [measured in degrees] on CBCT)												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	95	99	—	MD **3.88 degrees lower** (7 lower to 0.77 lower)	⨁⨁⨁⨁ High	Important
Coronal 3D bodily deviation (assessed with: Metric discrepancy [measured in mm] on CBCT)												
4	Randomized trials	Not serious	Serious[b]	Not serious	Serious[a]	None	95	99	—	MD 0.6 mm lower (1.21 lower to 0.01 higher)	⨁⨁◯◯ Low	Important
Apical 3D bodily deviation (assessed with: Metric discrepancy [measured in mm] on CBCT)												
4	Randomized trials	Not serious	Serious[b]	Not serious	Not serious	None	95	99	—	MD 0.75 mm lower (1.43 lower to 0.07 lower)	⨁⨁⨁◯ Moderate	Important
Postoperative pain (follow-up: median 7 d; assessed with: VAS (mm); Scale from: 0 to 100)												
3	Randomized trials	Serious[c]	Serious[b]	Not serious	Not serious	None	74	73	—	MD 17.09 mm lower (33.38 lower to 0.8 lower)	⨁⨁◯◯ Low	Important
Postoperative swelling (follow-up: median 7 d; assessed with: VAS (mm); Scale from: 0 to 100)												
2	Randomized trials	Serious[c]	Serious[b]	Not serious	Serious[d]	None	64	63	—	MD 6.59 mm lower (19.03 lower to 5.85 higher)	⨁◯◯◯ Very low	Important

Abbreviations: CBCT, cone beam computed tomography; CI, confidence interval; MD, difference in means; OIS, optimal information size; OR, odds ratio; VAS, visual analogue scale.

[a]The OIS criterion was met, but the 95% CI slightly overlapped no effect and at the same time it failed to exclude an important benefit (0.5 mm).

[b]High level of unexplained heterogeneity in the effect size.

[c]Most information is from studies at low/unclear risk of bias, but potential limitations are likely to lower confidence in the estimate of effect.

[d]The OIS was met, but the 95% CI clearly overlapped no effect and at the same time it failed to exclude an important benefit (10 mm).

and suggesting a safety margin of at least 2 mm. These errors may be even more relevant when sCAIP is applied flapless.

This systematic review was carried out following an "a priori" protocol registered on PROSPERO and in accordance with Cochrane Collaboration recommendations. Further data submission by the authors in three out of five studies allowed the realization of IPD analysis, which made meta-analyses feasible despite the small number of included trials, and enabled merging studies with different designs using proper estimates (ie, adjusted for split-mouth and/or clustering). Moreover, data on nonpublished outcome results were provided by authors, thus minimizing the risk of selective reporting bias. Finally, publication bias risk was reduced by searching unpublished trials in the gray literature.

Several limitations should, however, be considered when interpreting the results of the current systematic review. Despite the extensive literature search, only five RCTs fulfilling the inclusion criteria were found. The overall risk of bias evaluation was frequently not considered as low, and only one trial reported data with a follow-up longer than 12 weeks. Moreover, clinically meaningful outcomes (eg, biologically/prosthetically correct positioning, long-term implant survival and success), were lacking. This may be relevant, because despite the benefits in accuracy demonstrated in this systematic review when comparing flapless sCAIP with flapped FHIP/cPGIP surgeries, these differences may potentially have no impact on the long-term prognosis of placed implants. Additional limitations worth mentioning are the moderate/high level of heterogeneity present in most meta-analyses that was not always explained by subgroup analyses (even if calculations of heterogeneity values may be questionable because of the small number of trials included), the wide prediction intervals (which indicate that flapless sCAIP may not be beneficial in some settings), and the limited external validity attributable to the inclusion criteria and methods employed in the included trials (eg, no need for bone augmentation, most evidence coming from tooth-supported guides, and no evidence about flapless dCAIP).

5 | CONCLUSIONS

In conclusion, when considering the surgical invasiveness and the accuracy of implant placement with respect to the planned position, this systematic review has shown improved outcomes when using flapless sCAIP. Indeed, on one hand, flapless sCAIP seems to be associated with the reduced invasiveness distinctive of flapless approaches, specifically to a shorter surgical time, and to less intraoperative and postoperative morbidity (very low/low certainty). On the other hand, it preserves and even maximizes the short-term efficacy outcomes characterizing fully guided surgeries, especially in terms of accuracy with respect to the planned implant position (moderate/high certainty). However, whether these advantages have any potential impact on more meaningful long-term efficacy outcomes is yet to be determined.

When considering the use of flapless sCAIP, clinicians are, however, advised to make a proper case selection, restricting those procedures to cases characterized by the presence of a sufficient amount of keratinized tissue and no need for bone augmentation. Moreover, despite being associated with better accuracy than flapped FHIP/cPGIP, clinicians should consider that flapless sCAIP is still associated with some inaccuracies with respect to the planned implant position. Accordingly, and considering the meta-analytic measures of dispersions, a prudent safety margin of around 2 mm in depth, 3 mm in coronal and apical three-dimensional bodily position, and 4 degrees in angulation, may be recommended when applying sCAIP flapless. Finally, clinicians should consider that realizing flapless sCAIP procedures requires a learning curve for managing all the preoperative and intraoperative procedures associated with this approach (eg, three-dimensional planning). All these factors should be weighed up on a case-by-case basis.

The findings of this systematic review also highlight the need for future research in this field. Priority should be given to design RCTs comparing flapless dCAIP with flapped FHIP/cPGIP. Moreover, long-term data on flapless sCAIP vs flapped FHIP/cPGIP are needed, specifically on implant survival, success, the incidence of peri-implant diseases, and long-term costs.

ACKNOWLEDGMENTS

The authors are extremely grateful to Gabriel Magrin, Nichlas Nicchio, and Faris Younes for providing more information about their trials, as well as the requested additional data analyses and/or IPD. Moreover, the authors would like to kindly thank Volkan Arisan, Lauren Bernard, Gábor Braunitzer, Nancy Clelland, Sigmar Schnutenhaus, and Tommie Van de Velde for the information they provided about their published or ongoing trials, regardless of the final decision whether to include them in the current systematic review. Finally, the authors wish to thank Mustafa Tattan and Leandro Chambrone for the kind information provided about their systematic review on a similar topic, as well as Crystal Marruganti and Georgios Antonoglou for their precious help during data synthesis.

CONFLICT OF INTEREST

There were no conflicts of interest in relation to this systematic review.

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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Romandini M, Ruales-Carrera E, Sadilina S, Hämmerle CHF, Sanz M. Minimal invasiveness at dental implant placement: A systematic review with meta-analyses on flapless fully guided surgery. *Periodontol 2000*. 2023;91:89-112. doi: 10.1111/prd.12440