

# The Effect of Antihypertensive Agents on Dental Implant Stability, Osseointegration and Survival Outcomes: A Systematic Review

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**Abstract:** Antihypertensive agents are commonly prescribed to manage hypertension and are known to be beneficial for bone formation and remodeling. The aim of this systematic review was to assess the impact that antihypertensive agents have on dental implant stability, osseointegration, and survival outcomes. A review of the literature was conducted using articles from 11 data sources. PRISMA guidelines were followed, and a PICO question was constructed. The search string “Antihypertensive\* AND dental implant\* AND (osseointegration OR stability OR survival OR success OR failure)” was used for all data sources where possible. The Critical Appraisal Skills Programme (CASP) was used for study appraisal, including the risk of bias. The search resulted in 7726 articles. After selection according to eligibility criteria, seven articles were obtained (one randomized control trial, two prospective cohort studies, three retrospective cohort studies, and a case control study). Five papers investigated the effects of antihypertensive agents on primary stability, but there were discrepancies in the method of assessment. Inhibition of the renin–angiotensin–aldosterone system was linked to higher primary stability. Secondary stability was usually higher than primary stability, but it is unknown if antihypertensive agents caused this. Survival outcomes were increased with certain antihypertensive agents. It is possible that inhibition of the renin–angiotensin–aldosterone system may lead to greater bone mineral density, improved primary stability, and improved survival outcomes although the effects on osseointegration are unknown. However, more research is needed to confirm this theory.

**Keywords:** antihypertensive; dental implant; stability; osseointegration; survival



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## 1. Introduction

In the UK, once over a third of the population was edentulous; this figure is now closer to 6% nowadays [1–3]. This has led many, particularly the older generation over 50, to explore dental implants as a replacement option for missing teeth [4–6]. Managing patients within this age bracket comes with a unique set of problems, which can include reduced plaque control, poor oral health, and polypharmacy [7–11]. Many commonly prescribed medications are known to have a negative effect on dental implants, such as proton pump inhibitors and selective serotonin reuptake inhibitors [12–15]. There is evidence to suggest that antihypertensive (AH) agents may also have an effect on dental implants [16,17].

AH agents are used for the management of hypertension. Hypertension refers to consistently raised blood pressure and can negatively affect health [18]. It increases the risk

of heart, brain, and kidney damage, leading to poorer health outcomes (WHO, 2022). The World Health Organisation estimates that over 1.2 billion adults worldwide have hypertension, with almost half unaware they have the condition (WHO, 2022). The European Society of Hypertension and The European Society of Cardiology recommend five drug groups for the management of hypertension: Beta blocker (BB), Calcium channel blocker (CCB), Angiotensin receptor blocker (ARB), Angiotensin converting enzyme (ACE) inhibitor, and Thiazide diuretic (TD)

Previous research has shown interesting results regarding the use of AH agents and their effects on bone. Rejnmark et al. found beta blockers (BB), angiotensin converting enzyme (ACE) inhibitors, and calcium channel blockers (CCB) were shown to have a protective effect on bony fracture [19]. There is also evidence to suggest that AH agents show anabolic properties regarding bone metabolism and can even increase bone mineral density within the mouth [20,21]. It is possible that this effect on bone may lead to improved osseointegration and overall survival.

When assessing the success of an implant [22], developed criteria that are recognized as the gold standard for implant survival. The five criteria described by (Albrektsson et al., 1986) [22] are as follows: No mobility, no evidence of periapical radiolucency as seen on a radiograph, vertical bone loss of <0.2 mm yearly after the first year of service, absence of signs of pain, infection, neuropathies, paraesthesia, or violation of the mandibular canal, success rate of 85% and 80% at the end of 5 years and 10 years of functioning

Stability and osseointegration of the implant are paramount to success, according to Albrektsson. Adequate primary stability improves the chances of successful osseointegration, leading to better outcomes [23]. Primary stability is achieved when an implant is firmly placed within the cortical bone. At this stage, the bone and implant are held together by friction instead of integration. Secondary stability, also known as osseointegration, occurs a few months later when the bone fuses with the implant. There are various methods to assess implant stability, including resonance frequency analysis and insertional torque testing for primary stability, and resonance frequency analysis, reverse torque testing, histologic analysis, and radiographs or computed tomography for secondary stability.

The aim of this review is to assess the impact AH agents have on dental implant stability, osseointegration, and survival outcomes through a review of the relevant literature. The rationale for this review emerges from clinical observations and a burgeoning interest in how systemic medications influence dental treatment outcomes. Specifically, the use of AH drugs has been associated with alterations in blood flow and angiogenesis, processes that are fundamental to the healing and integration of dental implants. Furthermore, the potential effects of AH drugs on bone metabolism and the inflammatory response present a complex interplay that could significantly impact implant success rates.

## 2. Materials and Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered with PROSPERO CRD48209589262.

### 2.1. Eligibility Criteria

The following eligibility criteria were developed for the review:

#### 2.1.1. Inclusion

All adults (18 or over)

Any number of endosseous dental implants fitted within the maxilla or mandible

Research was published from October 2001–October 2024. This is to exclude older-design implants, such as those with smooth/polished surfaces or those without surface treatment [24–26].

Original studies (any prospective or retrospective cohort, case-control, cross-sectional, or randomized controlled trials looking at the effects of AH drugs on dental implants)

Any AH agent and its interaction with dental implants.

### 2.1.2. Exclusion

Letters/editorials

Posters

Prototype implants

Participants were under 18 years old at the time of the study

Animal studies

Studies are not conducted in English.

Case reports

Systematic reviews

Studies published before October 2001

Zygomatic and pterygoid implants

The following PICO framework was used to structure the clinical question:

Population: An adult population (over 18 years of age), of any medical background, undergoing treatment with any number of AH agents.

Intervention: Dental implants fitted within the maxilla or mandible to be restored with any prostheses.

Comparison: Individuals with dental implants who are not taking AH agents.

Outcomes: Effect on dental implant stability, osseointegration, and survival outcomes

Articles were divided into three groups for synthesis, depending on the content. The headings of these groups were: stability, osseointegration, and survival outcomes. Eleven databases plus relevant 'grey' literature and a manual search were identified as sources of information.

The following information sources were identified as containing relevant articles:

PubMed, Wiley Online Library, SCOPUS, Google Scholar, VHL Regional Portal, LILACS, Cochrane database, OVID, Dental Update, Journal of Dental Research, International Journal of Oral and Maxillofacial Surgery, EMBASE, EBSCO, and Web of Science.

### 2.1.3. Search Strategy

In order to generate a useful search string, "Antihypertensive\* AND dental implant\* AND (osseointegration OR stability OR survival OR success OR failure)" was used for all databases but had to be adapted for Dental Update in order to obtain sufficient results. The search strategy for each information source is described above.

This revealed 7726 articles that could meet the aim of this study.

Studies were screened by title, abstract, full text available, and full text screening. The final report generated seven records for discussion. For a visualization of the selection process, please refer to the Prisma Flowchart at the end of this section (Figure 1).

The critical Appraisal Skills Programme (CASP) was used for study appraisal, including the risk of bias. This system was used to assess the relevance of each paper. No papers were excluded after the CASP review. The primary outcomes of this review were to assess the effects of AH agents on dental implant stability, osseointegration, and longevity. The CASP tool version 2018 is used to systematically evaluate the trustworthiness, relevance, and results of published papers. The tool typically includes checklists that can be applied to qualitative, quantitative, and mixed-method research. These checklists help assess aspects like the clarity of research aims, appropriateness of methodology, transparency in reporting results, and significance of the findings, as can be seen in the Appendix A.

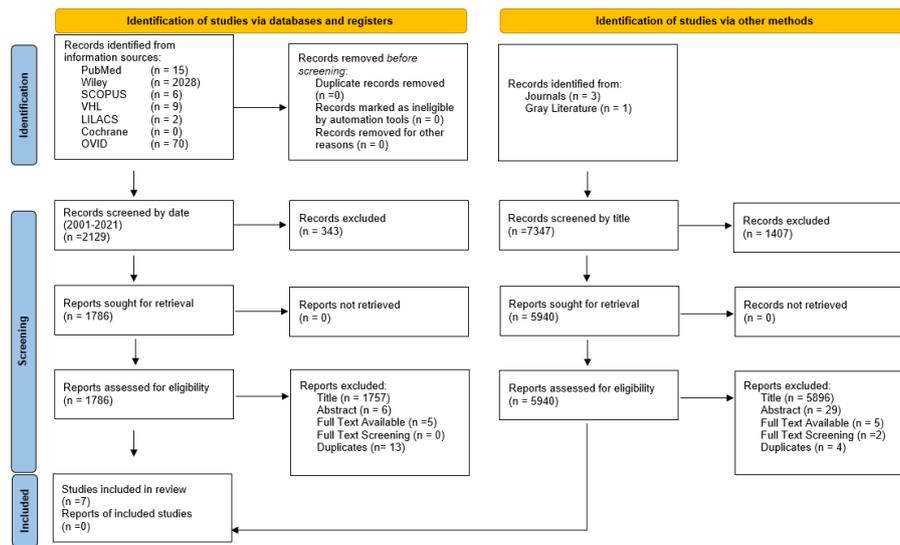


Figure 1. PRISMA flow chart.

### 3. Results and Discussion

This review identified one randomized control trial, two prospective cohort studies, three retrospective cohort studies, and a case control study. These studies, along with their results, can be seen in Table 1. The selected study discussion will focus on three main sections: primary stability, secondary stability (osseointegration), and survival outcomes.

In performing the risk of bias assessment [27], the study displayed moderate risk due to limitations in the blinding of participants to the intervention.

Carr et al., 2019 [15] showed a low risk of bias; the study methodology was robust with clear data collection and analysis procedures.

Wu et al., 2016 [17] presented a high risk of bias due to selective reporting and incomplete outcome data. Seki et al., 2020 [28] demonstrated a low risk of bias with comprehensive data reporting and analysis.

Garcia-Denche et al., 2013 [29] displayed Moderate risk due to an inadequate sample size, which could affect the generalizability of the results. Malm et al., 2021 presented Low-risk: the study used a strong experimental design with clear, transparent reporting. Alam-Eldein et al., 2017 [30] noted a high risk due to potential conflicts of interest and a lack of participant blinding.

Table 1. (a) Study the characteristics of patients taking different classes of antihypertensive drugs with reference to their bone density, plaque, gingival index, probing depth, and marginal bone loss. (b) Effect of antihypertensive drugs on primary and secondary stability and their effect on implant survival, success, and failure.

(a)										
Authors and Publication Year	Study Type	Aim	Antihypertensives Investigated	Number of Implants	Number of Participants	Bone Density/ Formation/ Quality	Plaque Control Index	Gingival Index	Probing Depth	Marginal Bone Loss
Saravi et al. (2021) [27]	Retrospective cohort	Investigate antihypertensive drug use on primary and secondary implant stability	BBs, RAS inhibitors, combination	377	196	Not mentioned	Not mentioned	Not measured	Not measured	Not measured

Table 1. Cont.

(a)										
Authors and Publication Year	Study Type	Aim	Antihypertensives Investigated	Number of Implants	Number of Participants	Bone Density/Formation/Quality	Plaque Control Index	Gingival Index	Probing Depth	Marginal Bone Loss
Saravi et al. (2021) [27]	Retrospective cohort	Investigate antihypertensive drug use on primary and secondary implant stability	BBs, RAS inhibitors, combination	377	196	Not mentioned	Not mentioned	Not measured	Not measured	Not measured
Wu et al. (2016) [17]	Retrospective cohort	Investigate the association between antihypertensive drugs and the survival rate of osseointegrated implants	BB, TD, ACE inhibitors, ARBs, other drugs (not specifically mentioned)	1499	728	Not mentioned	Not mentioned	Not measured	Not measured	Not measured
Carr et al. (2019) [15]	Prospective cohort	Identify associations between implant failure and medication use in a cohort of consecutive patients	CCB	Not mentioned	548	Not mentioned	Not mentioned	Not measured	Not measured	Not measured
Seki et al. (2020) [28]	Retrospective cohort	Investigate the effect of antihypertensive agents on peri-implant health	CCB, ARB, TD, combination	77	35	Not mentioned	AH > HNU	AH > HNU	AH > HNU	AH > HNU
García-Denche et al. (2013) [29]	Split mouth, two arm randomized control trial	To evaluate the effect of membrane coverage on anrostomy defects on implant survival in sinus lift procedures	Not mentioned	Two arm study—278 implants	Two arm study—104 participants, Split mouth group—5	Mean new bone percentage was greater when membrane was used ( $19 \pm 6$ ) compared to not used ( $15 \pm 5$ )	Not mentioned	Not measured	Not measured	Not measured
Malm et al. (2021) [31]	Retrospective case control	To identify possible risk factors for early implant failure	Not mentioned	25,825	182	Bone volume odds ratio 9.07, $p < 0.05$ Bone quality 1.53, $p > 0.3$	Not mentioned	Not measured	Not measured	Not measured
Alam-Eldein et al. (2017) [30]	Prospective cohort	To compare the effects of Calcium channel-blocking agents (Amlodipine) and angiotensin receptor blockers (Valsartan) on dental implant health	CCB (amlodipine), ARB (valsartan)	40	20	Not mentioned	ARB has better plaque control than CCB (trend from insertion to 24-month review)	ARB has less gingival bleeding than CCB (trend from insertion to 24-month review)	ARB has reduced probing depths than CCB (trend from insertion to 24-month review)	ARB has less marginal bone loss than CCB (trend from insertion to 24-month review)

Table 1. Cont.

(b)					
Authors and Publication Year	Measure of Stability	Primary Stability	Secondary Stability / Osseointegration	Effect on Success, Survival or Failure	Follow Up
Saravi et al. (2021) [27]	Resonance frequency analysis (ISQ, Ostell) High—>70 Medium—60–69 Low—<60	HNU—71.8 ± 8.7 AH—74.1 ± 5.6 Subgroups: BB—71.7 ± 5.4 Combined 77 ± 5.5 RAAS Inhibitor 74.52 ± 5.2	HNU—73.7 ± 8.1 AH—75.7 ± 5.9 Subgroups: BB—72 ± 6.4 Combined 78.36 ± 5.1 RAAS Inhibitor 76.64 ± 5.6	Not mentioned	120 days
Wu et al. (2016) [17]	Insertional torque	AH users had 218 implants (66.7%) > 35 Ncm IT and 105 implants (32.1%) had <35 Ncm IT. HNU had 721 (61.5%) > 35 Ncm while 369 implants (31.5%) < 35 Ncm. AH > IT	Not mentioned	AH 99.6% survival HNU—96.9% survival	17.1 months
Carr et al. (2019) [15]	Not mentioned	Not mentioned	Not mentioned	CCB not associated with improved survival outcomes or increased risk of failure	Median—5.8 years for surviving implants and 0.6 years for implant failure
Seki et al. (2020) [28]	Not mentioned	Not mentioned	Not mentioned	Not mentioned	7 years 1 month
García-Denche et al. (2013) [29]	Not mentioned	Simultaneous implant placement is less likely to achieve primary stability compared to a delayed approach (odds ratio 15.53 $p < 0.04$ )	Not mentioned	Success with AH—89% Success without AH—87%	12 years
Malm et al. (2021) [31]	Not mentioned	Low primary stability associated with increased likelihood of early implant failure (odds ratio 3.04 $p < 0.001$ )	Not mentioned	No link between AH and early implant failure	1 year
Alam-Eldein et al. (2017) [30]	RFA (ISQ, Ostell) Values < 50 have a greater risk of failure	ARB—56.025 ± 3.206 CCB—55.625 ± 4.428	6 months—ARB—58 ± 3.424, CCB—57.57 ± 3.238 12 months—ARB—58.975 ± 5.2223, CCB—58.075 ± 6.442 24 months—ARB—60.2 ± 3.4, CCB—60.1 ± 2.768	No implants lost in study. No association of CCB/ ARB with increased risk of failure	24 months

### 3.1. Primary Stability

Five of the seven papers identified in this review investigated the effect of primary stability on dental implants [17,27,29–31]. Primary stability is the wedging effect that occurs when an implant is initially placed in bone. The implant is held by frictional forces rather than osseointegration, which occurs during secondary stability. Saravi et al. [27] and Alam-Eldein et al. [30] assessed primary stability by resonance frequency analysis, while Wu et al. used the insertional torque test [17].

Wu et al. [17] report that insertional torque is not associated with an increased risk of implant failure when comparing those medicated with AH agents to HNU. Approximately one-third of the AH and HNU cohorts had an insertional torque of <35 Ncm, while the remaining two-thirds had >35 Ncm. As a result of both groups experiencing the same ratios of insertional torque, this was not shown to have an effect on survival outcomes.

Studies conducted by Malm et al. [31] and Garcia-Denche et al. [29] report that participants were medicated on AH agents, so no deductions can be made relating to AH use. Alam-Eldein et al. [30] and Saravi et al. [27] investigated primary stability using resonance frequency analysis. Both studies concluded that patients medicated on ARBs had higher primary stability than the comparison groups. Only the results obtained by Saravi et al. [27] were shown to be statistically significant. These results should be viewed with caution due to the low number of ARBs included within their sample (9/22) with the remainder being ACE inhibitors. This would suggest that improvements in stability could be linked to inhibition of the renin–angiotensin–aldosterone system (RAAS).

Saravi et al. [27] demonstrated that diameter was shown to be a statistically significant factor leading to increased implant stability (4.1 mm/4 mm > less than 4 mm). Other factors linked to improved stability are the type of implant (Straumann > Thommen) and region placed (maxilla > mandible). The higher primary stability achieved by the ARB group could be explained by these factors, as 93.5% of implants within this group had a diameter of 4 mm/4.1 mm when compared to 81.9% in HNU. This is supported by Barikani et al. [32], who found that increasing implant diameter from a narrow platform (3.4 mm) to regular (4.3 mm) led to an increase in the implant stability quotient. Interestingly, in their study, they found this relationship did not exist when further increasing a regular platform to a wide platform and incurred a decrease in stability. This may be explained by a loss of available bone by increasing the width of the osteotomy. This could also explain the difference in values obtained from Saravi et al. [27] and Alam-Eldein et al. [30], as Alam-Eldein et al. [30] used narrow-diameter implants, which led to a reduction in stability when compared to Saravi et al. [27]. A comparison of the two would suggest that implant diameter has an effect on primary stability. While the effect of AH agents is still controversial, it is likely that inhibition of the renin–angiotensin–aldosterone system by renin angiotensin aldosterone system inhibitors will have an effect on bone remodeling.

### 3.2. Secondary Stability (Osseointegration)

Secondary stability (osseointegration) was assessed by Alam-Eldein et al. [30] and Saravi et al. [27] using resonance frequency analysis. The results of both studies demonstrated that secondary stability is greater than primary stability when the implant has successfully osseointegrated. This is likely due to the remodeling process that occurs during osseointegration, which anchors the implant to bone. Both studies did not include a histologic analysis as part of their measure of osseointegration, and so we are unable to measure the bone-to-implant contact percentage of the implants, but its relevance to osseointegration should be discussed.

Folkman et al. [33] found that bone-to-implant contact increased over a 3 week period in implants placed in rabbit tibias. It is not clear whether this increase in contact percentage led to an increase in secondary stability, as this was not an outcome measure. Jung et al. [34] evaluated the contact percentage of implants used as anchorage devices for orthodontic treatment. They found that 42% is enough to establish and maintain osseointegration. The implants used in the study were under relatively low forces, 2 N–6 N, compared to implants used to functionally replace teeth [34]. Interestingly, the contact percentage of implants within this study was not dissimilar to those reported by Linares et al. [35], who measured bone-to-implant contact in immediate and early-loaded implants in an animal model. Based on these studies, it is unclear if loading forces have a positive effect on contact percentage, although we can postulate that a larger contact percentage would lead to higher levels of stability and greater osseointegration.

Several factors have been linked to increased secondary stability, such as healing time and primary stability [36]. Secondary stability takes around 4 weeks to occur, during which time a decrease in implant stability is known to occur, known as the ‘stability gap’ [37]. During this time, the bone remodels and is relatively weak compared to fully mineralized bone. Failure is more likely to occur due to the increased micromotion experienced by the implant, and so higher ISQ values are better able to withstand these destabilizing forces [38,39]. Achieving an implant stability quotient between 60 and 70 can reduce micromotions by 50%, allowing for better osseointegration [30]. Alam-Eldein et al. [30] used immediate loading for their implants, while Saravi et al. [27] used implants that were buried until exposure. Immediately loaded implants would be expected to experience greater micromotion and failure, which did not occur in this study. This expectation would be enhanced by a low implant stability quotient (ISQ) at placement (<60), but could be accounted for by the small number of implants used within the study [32] or low occlusal forces acting on the implants by an upper complete denture (which was

constructed alongside the lower implant-supported denture), and so this may not be a reliable assessment of results.

Both studies gave adequate time to allow osseointegration to occur. Saravi et al. [27] measured secondary stability at  $117 \pm 56.6$  days, while Alam-Eldein et al. [30] reviewed stability measurements at 6 month intervals up to 2 years. In both studies, implant stability quotient values increased over time. Saravi et al. [27] showed that renin–angiotensin–aldosterone system (RAAS) inhibitors had the highest ISQ values (outside of the combined group, which failed to reach significance due to a low sample), which echoed results from Alam-Eldein et al. [30]. This is similar to the primary ISQ results obtained during the assessment of primary stability. This is logical, as primary stability is an excellent predictor of secondary stability and osseointegration [40,41].

### 3.3. Survival Outcomes

Five papers considered the link between AH agents and survival outcomes [17,27,29–31]. Wu et al. [17] and Garcia-Denche et al. [29] found that patients who were medicated on AH agents had improved survival outcomes when compared to those who were unmedicated, and it could be due to the possibility that the renin–angiotensin–aldosterone system is actually the cause of these changes in the bone cellular capacity in favor of implant integration, Garcia-Denche et al. [29] do not reveal which agents were included in their study, which limits further discussion on the effect of each subgroup.

Reported long-term survival rates of dental implants range from 93.3 to 98% [42–44]. The survival rate of those medicated on AH agents (99.6%) in the study by Wu et al. [17] exceeds this range, but this may be explained by a smaller sample size and reduced follow-up time. Those unmedicated reached a survival rate of 96.9%, which is within the parameters of a good survival outcome. One possible risk of medicating a normotensive person would be the increased risk of hypotension and resultant falls. Although the literature would suggest those medicated with certain AH agents would have a reduced risk of a bony fracture, the patient would still be liable for other risks of falling: skin abrasions, lacerations, head injuries, etc. These risks may not outweigh the benefits of medication, considering the high survival rate regardless of treatment. It is worth noting that the survival rates of both AH users/HNU were significantly lower in the trial by Garcia-Denche et al. [29] when compared to Wu et al. [17].

Garcia-Denche et al. [29] opted for a combination of simultaneous and delayed implant placement. It is accepted that it is more difficult to achieve adequate levels of primary stability during simultaneous placement when compared to a delayed approach due to the differing levels of bone density, and as such, we would expect studies consisting exclusively of simultaneous placement to have relatively low levels of implant survival. However, it is worth noting that immediate implant placement offers several advantages over a delayed approach, such as reduced overall surgical time, which is beneficial to both clinician and patient. It also allows a relative preservation of both hard and soft tissue, although some reduction is to be expected due to the loss of the periodontal ligament, which acts as a blood supply for the surrounding tissue [45,46].

Cha et al. [47] managed to achieve a survival rate of 98.91% during a follow-up period of 57.1 months—nearly five times longer than Garcia-Denche et al. [29]. The differences between the two studies may be explained by the sample size. Garcia-Denche et al. [28] included 19 patients who were medicated on AH agents while 85 were not. In comparison, Cha et al. [47] recruited 161 patients. A small sample results in each patient representing a larger overall percentage of the total, and so failures have a greater effect on overall survival, thus increasing the effects of sample bias. Wu et al. [17] included five subgroups of AH agents: ACE inhibitors, ARBs, TDs, BBs, and “other drugs”. Interestingly, 54% of patients included in the study were medicated on RAAS inhibitors (which include ACE inhibitors and ARBs). It is prudent to remember that previous studies have found that inhibition of the RAAS has been linked to greater implant stability, which in turn leads to better osseointegration and improved survival outcomes [24,25,30]. It could be

that including a large proportion of RAAS inhibitors led to greater survival outcomes. However, the patients within this study were followed up for just over 17 months, so mid- to long-term survival is unknown.

Malm et al. [31], in their case control study, found that AH agents were not linked to early implant failure (failure within 1 year of functioning). Small numbers were included in both the AH group and the control group, which limits the validity of the results. Furthermore, the study was a case control, so a causal link cannot be produced.

Carr et al. [15] and Alam-Eldein et al. [25] both found that CCBs were not linked to an increased risk of implant failure. Alam-Eldein et al. [30] included a relatively low, heterogeneous sample size of 20 males, while [15] included an improved sample of 548 men and women. Carr et al. [15] do not include any data regarding region of placement, implant length/diameters, loading protocol, or bone quality, all of which have an effect on implant survival. As such, it is difficult to explore any reasons behind their results. The results by Alam-Eldein et al. [30] may be explained by all implants being placed within the mandible, which, as discussed earlier, has a higher chance of survival than the maxilla. All implants were fitted with an overdenture and occluded against an upper denture, which, due to the reduced contact forces when compared to natural teeth, is favorable for success [23]. Additionally, Mishra et al. 2023 [48], in their systematic review, aimed to compare the clinical outcomes of dental implants in individuals using antihypertensive medications versus non-users. The databases suggested by studies involved a total of 959 patients, primarily using renin–angiotensin system (RAS) inhibitors. Findings indicated that the implant survival rate was notably higher in users of antihypertensive medications (99.4%) compared to non-users (96.1%). Additionally, a study within this review reported greater implant stability quotient (ISQ) scores in medicated patients ( $75.7 \pm 5.9$ ) than in non-medicated patients ( $73.7 \pm 8.1$ ). Despite these positive outcomes, the evidence remains limited and heterogeneous, particularly regarding the specific types of antihypertensive medications used. As such, more targeted research is necessary to isolate the effects of different antihypertensive drugs on dental implant success and stability [48].

The varying levels of risk of bias across the studies critically influence the systematic review's overall conclusions. For studies like Wu et al., 2016 [17], and Alam-Eldein et al., 2017 [30], the high risk of bias might undermine the reliability of their conclusions, suggesting a potential overestimation or underestimation of the treatment effects. Conversely, studies with a low risk of bias, such as Carr et al., 2019 [15], and Malm et al., 2021 [31], provide stronger evidence and add more weight to the systematic review's findings. The mixed levels of bias underscore the necessity for cautious interpretation of the overall evidence and highlight the importance of considering bias in the aggregation of study results [48].

#### 4. Conclusions

It is possible that inhibition of the renin–angiotensin–aldosterone system may lead to greater bone mineral density, improved primary stability, and improved survival outcomes for dental implants. There are, however, several animal studies that indicate that AH agents, especially BBs such as propranolol, may increase the amount of BIC experienced during. This will likely lead to a stable implant due to increased surface attachment and may possibly have an effect on long-term survival. More research is required to investigate the effects of antihypertensive drugs on the higher survival rate of dental implants.

The potential inhibition of the renin–angiotensin–aldosterone system may contribute to an increase in bone mineral density, which could enhance the primary stability and survival outcomes of dental implants.

The findings indicate that inhibition of the renin–angiotensin–aldosterone system is positively associated with the higher primary stability of dental implants. While secondary stability generally exceeded primary stability, the direct influence of antihypertensive agents on this aspect remains unclear. Moreover, some antihypertensive agents were associated with improved survival outcomes for implants. Despite these promising results, discrepancies in the assessment methods of primary stability and limited data on osseointe-

gration highlight the need for further research. Future studies should aim to standardize evaluation techniques and expand the understanding of how antihypertensive agents affect implant success over time.

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### Appendix A

Appendix A.1 (Saravi et al., 2021) CASP Appraisal



Impact of renin-angiotensin system inhibitors and beta-blockers on dental implant stability  
 Paper for appraisal and reference:.....

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: A question can be 'focused' in terms of

- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

Comments:

The study was ascertaining whether antihypertensive medications, used alone or in combination with other antihypertensive drugs, had an effect on dental implant stability. This was compared to a control group. The population investigated was indicative of the population that usually receives dental implant treatment.

2. Was the cohort recruited in an acceptable way?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for selection bias which might compromise the generalisability of the findings:

- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

Comments:

The cohort of participants were recruited from a single centre using retrospective data. The median age of the cohort was 65 which is in line with other studies of this nature. There was a near even split of males to females (100 males and 96 females). The study was investigating dental implant stability and required that participants be periodontally stable as this may be a confounding factor. There was a clear inclusion and exclusion criteria.

Is it worth continuing?



3. Was the exposure accurately measured to minimise bias?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments:

Participants were divided into 4 groups: no history of antihypertensive drug use, beta blockers (BB), renin angiotensin system (RAAS) blockers and combination. Dosing regimen and length of treatment for the antihypertensive drugs were not provided as part of the study although it is not clear whether this is of importance.

4. Was the outcome accurately measured to minimise bias?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
  - has a reliable system been established for detecting all the cases (for measuring disease occurrence)
    - were the measurement methods similar in the different groups
    - were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments:

All dental implants had their stability measured at insertion and 120 days after insertion. Measuring sites were the same for each implant (buccal and palatal aspect and an average recorded). Stability measurements were recorded using radiofrequency analysis.



5. (a) Have the authors identified all important confounding factors?

Yes	X
Can't Tell	
No	

HINT:  
 • list the ones you think might be important, and ones the author missed

Comments:  
 Confounders mentioned: age, sex, length and diameter of implant, maxilla vs mandible, if grafting occurred or sinus augmentation.  
 No discussion on what type of bone the implant was placed i.e. D1,D2,D3,D4 as this may affect stability.

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes	X
Can't Tell	
No	

HINT:  
 • look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:  
 Confounders compared in results and discussed if statistically significant or not.

6. (a) Was the follow up of subjects complete enough?

Yes	X
Can't Tell	
No	

HINT: Consider  
 • the good or bad effects should have had long enough to reveal themselves  
 • the persons that are lost to follow-up may have different outcomes than those available for assessment  
 • in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes	X
Can't Tell	
No	

Comments:

In most situations, 120 days would be an appropriate length of follow up to assess secondary stability for a dental implant but this can be elongated in cases of sinus augmentation. The paper may have a secondary outcome to assess if 120 days is an appropriate length of time to then load an implant after having sinus surgery but this was not discussed.

Section B: What are the results?

7. What are the results of this study?

- HINT: Consider
- what are the bottom line results
  - have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
  - how strong is the association between exposure and outcome (RR)
  - what is the absolute risk reduction (ARR)

Comments:

RAAS inhibitors are associated with higher implant stability (primary and secondary) than the control group. There was no significant difference between BB and control group. The combined group had a very high ISQ (stability measurement) but this failed to reach significance due to the low sample size.

8. How precise are the results?

- HINT:
- look for the range of the confidence intervals, if given

Comments:

Results are precise owing to the objective method of scoring implant stability.



9. Do you believe the results?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- big effect is hard to ignore
  - can it be due to bias, chance or confounding
  - are the design and methods of this study sufficiently flawed to make the results unreliable
  - Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments:  
 Results are plausible and were explained in the discussion section. I would have expected BB to have achieved higher ISQ values than the control group owing to their anabolic effect on bone but they were still comparable to native bone in non users which is believable.

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider whether
- a cohort study was the appropriate method to answer this question
  - the subjects covered in this study could be sufficiently different from your population to cause concern
  - your local setting is likely to differ much from that of the study
  - you can quantify the local benefits and harms

Comments:  
 A cohort study was an appropriate way of conducting this paper and its results can easily be applied to any UK population.

11. Do the results of this study fit with other available evidence?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

Comments:  
 No other similar studies exist in measuring ISQ in antihypertensive drug users.



12. What are the implications of this study for practice?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
    - for certain questions, observational studies provide the only evidence
    - recommendations from observational studies are always stronger when supported by other evidence

Comments:  
 More research needed in this area. It would be beneficial to have a range of antihypertensive drug users and in greater sample size.

Appendix A.2 (Carretal., 2019) CASP Appraisal



Paper for appraisal and reference: Risk of Dental Implant Failure Associated With Medication Use

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: A question can be 'focused' in terms of
- the population studied
  - the risk factors studied
  - is it clear whether the study tried to detect a beneficial or harmful effect
  - the outcomes considered

Comments:  
 Aims of the study are clearly identifiable - to determine if any medication use is linked to a higher probability of dental implant failure. This data was taken from a single centre from 1983 - 2014.

2. Was the cohort recruited in an acceptable way?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Look for selection bias which might compromise the generalisability of the findings:
- was the cohort representative of a defined population
  - was there something special about the cohort
  - was everybody included who should have been

Comments:  
 The cohort were recruited from a single centre using retrospective data from 1983 - 2014. Each patient was receiving their first dental implant and data was recorded based on having medication treatment started before implant placement or after implant placement. Those not followed up were excluded from the results. No clear exclusion criteria.

Is it worth continuing?



3. Was the exposure accurately measured to minimise bias?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments:

Patients were followed up from date of first implant placement to the date of their last follow up or when their first implant failed. They were then exposed to a drug. This exposure could be pre-dating the implant placement or after implant placement. It is unclear how long patients were medicated for pre-implant placement and if this had an effect on failure. No clear definition of what implant failure is. Only investigated calcium channel blockers (CCBs) for antihypertensive medications which is of little use as there are many classes of antihypertensive medications.

4. Was the outcome accurately measured to minimise bias?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
  - has a reliable system been established for detecting all the cases (for measuring disease occurrence)
    - were the measurement methods similar in the different groups
    - were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments:

Patients were followed up from date of first implant placement to the date of their last follow up or when their first implant failed. They were then exposed to a drug. This exposure could be pre-dating the implant placement or after implant placement. It is unclear how long patients were medicated for pre-implant placement and if this had an effect on failure. No clear definition of what implant failure is.



5. (a) Have the authors identified all important confounding factors?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input checked="" type="checkbox"/>

HINT:  
 • list the ones you think might be important, and ones the author missed

Comments:

No clear exclusion criteria which can lead to bias as many confounding factors have not been mentioned. For example, periodontal disease, smoking and uncontrolled diabetes have not been discussed and have been linked to increased dental implant failure.

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input checked="" type="checkbox"/>

HINT:  
 • look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:

The authors have adjusted for some confounding factors which may affect implant failure such as age, sex and era of implantation but have not allowed for many more such as smoking status, periodontal status and uncontrolled diabetes.

6. (a) Was the follow up of subjects complete enough?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- the good or bad effects should have had long enough to reveal themselves
- the persons that are lost to follow-up may have different outcomes than those available for assessment
- in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

Comments:

All patients not lost to follow up were reviewed up until implant failure. This is appropriate as the study is assessing factors which link to implant failure and so following up until failure is satisfactory. Median follow up for an implant which has not failed was 5.8 years. Median follow up until failure was 0.6 years.

Section B: What are the results?

7. What are the results of this study?

HINT: Consider

- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments:

No medications (including CCBs) were associated with an increased risk of dental implant failure. This included 548 patients on antihypertensive medications.

8. How precise are the results?

HINT:

- look for the range of the confidence intervals, if given

Comments:

Results give data for CCBs but do not include data for any other antihypertensive medication. They do not give data on what CCBs were used, dose or how long for. They also do not include what other medications the patient was on or discussion of any confounding factors that may lead to increased risk of implant failure.



9. Do you believe the results?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- big effect is hard to ignore
  - can it be due to bias, chance or confounding
  - are the design and methods of this study sufficiently flawed to make the results unreliable
  - Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments:  
Results are valid but too vague to be useful. They have a large sample of CCB users (548) but limited data on dosing, duration or other medications and confounders. Also no clear definition of failure or how this is assessed.

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider whether
- a cohort study was the appropriate method to answer this question
  - the subjects covered in this study could be sufficiently different from your population to cause concern
  - your local setting is likely to differ much from that of the study
  - you can quantify the local benefits and harms

Comments:  
  
Cohort study was an appropriate study design for this study but lacks necessary detail on antihypertensive use to be useful. I would image if repeated in a UK population, similar results would be obtained.

11. Do the results of this study fit with other available evidence?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

Comments:  
Wu et al 2016 found that antihypertensives led to increase dental implant survival while this study found no link. This may be because they looked at different classes of antihypertensive drugs.



12. What are the implications of this study for practice?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
    - for certain questions, observational studies provide the only evidence
    - recommendations from observational studies are always stronger when supported by other evidence

Comments:

CCBs may not be an effective drug for increasing dental implant survival outcomes. This study has only looked at one type of antihypertensive and has not investigated the doing regimen or time on the drug. We are also not aware of what the failure criteria was or the effect of confounders (smoking status, diabetes etc).

Appendix A.3 (Wu et al., 2016) CASP Appraisal



Antihypertensive Medications and the Survival Rate of Osseointegrated Dental Implants: A Cohort Study  
 Paper for appraisal and reference:.....

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: A question can be 'focused' in terms of
- the population studied
  - the risk factors studied
  - is it clear whether the study tried to detect a beneficial or harmful effect
  - the outcomes considered

Comments:

To investigate the association between antihypertensive (AH) drugs and the survival rate of osseointegrated implants. This is important as AH agents are commonly prescribed and some have an effect on bone. At present, there is no consensus if this effect on bone translates into a better survival outcome for dental implants, if any effect occurs.

2. Was the cohort recruited in an acceptable way?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Look for selection bias which might compromise the generalisability of the findings:
- was the cohort representative of a defined population
  - was there something special about the cohort
  - was everybody included who should have been

Comments:

Participants were recruited from a single centre "East Coast Oral Surgery" from 2007 - 2014. Participants were excluded if they have active periodontal disease or short implants less than or equal to 4mm. It is assumed these factors will have an effect on the survival outcomes. Retrospective data.

Is it worth continuing?

3. Was the exposure accurately measured to minimise bias?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments:

The exposure to these patients was having a dental implant or implants placed. Survival outcomes were measured rather than success rates. Failure criteria clearly defined. The variable is the AH agents that patients were medicated on.

4. Was the outcome accurately measured to minimise bias?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
  - has a reliable system been established for detecting all the cases (for measuring disease occurrence)
    - were the measurement methods similar in the different groups
    - were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments:

There is a clearly defined failure criteria which is subjective e.g. pain on function, mobility, implant no longer in mouth etc. All patients were followed up by a single implantologist who also placed all the implants.



5. (a) Have the authors identified all important confounding factors?

Yes	x
Can't Tell	
No	

HINT:  
 • list the ones you think might be important, and ones the author missed

Comments:  
 Confounders mentioned: age, gender, implants length and diameter, insertional torque, smoking status, controlled diabetes, bone augmentation, loading protocol, parafunctional habits  
 Not mentioned: how do they ascertain if a patient is a controlled diabetic? Short follow up time of 17 months average.

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes	x
Can't Tell	
No	

HINT:  
 • look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:  
 Multilevel survival analysis carried out for different factors which may affect survival.

6. (a) Was the follow up of subjects complete enough?

Yes	x
Can't Tell	
No	

HINT: Consider  
 • the good or bad effects should have had long enough to reveal themselves  
 • the persons that are lost to follow-up may have different outcomes than those available for assessment  
 • in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes	
Can't Tell	x
No	



Comments:

The study had no drop outs which ensures it has a complete set of patient data. However, there are concerns with an average follow up of 17 months.

Section B: What are the results?

7. What are the results of this study?

- HINT: Consider
- what are the bottom line results
  - have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
  - how strong is the association between exposure and outcome (RR)
  - what is the absolute risk reduction (ARR)

Comments:

Patients treated with AH agents had higher survival outcomes than those not treated with AH agents (control group). This was statistically significant. The study was unable to identify the specific influence of each AH agent due to limited sample sizes.

8. How precise are the results?

- HINT:
- look for the range of the confidence intervals, if given

Comments:

Results are statistically significant but cannot determine the influence of individual AH agent and so are of limited benefit.



9. Do you believe the results?

Yes	x
Can't Tell	
No	

- HINT: Consider
- big effect is hard to ignore
  - can it be due to bias, chance or confounding
  - are the design and methods of this study sufficiently flawed to make the results unreliable
  - Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments:  
Results are plausible but too vague to determine if they are useful regarding decision making for dental implants.

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	x
Can't Tell	
No	

- HINT: Consider whether
- a cohort study was the appropriate method to answer this question
  - the subjects covered in this study could be sufficiently different from your population to cause concern
  - your local setting is likely to differ much from that of the study
  - you can quantify the local benefits and harms

Comments:  
Subjects in this study had an average age of 57 and an even split of males to females. This is comparable to the population of patients who would want a dental implant.

11. Do the results of this study fit with other available evidence?

Yes	
Can't Tell	x
No	

Comments:  
I am unaware of any other studies that have assessed Ah medication and dental implant survival outcomes in this way. As such, comparison is not achievable.



12. What are the implications of this study for practice?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
  - for certain questions, observational studies provide the only evidence
  - recommendations from observational studies are always stronger when supported by other evidence

Comments:  
 More evidence required to bolster their conclusions. This could be achieved by having a larger population of patients to be recruited from multiple centres. The distribution of AH agents is also skewed in favour of ACE inhibitors and ARBs which comprise over 50% of the AH agents. In future, this should be evenly split. A longer follow up time for 5 to 10 years would also help validate the results.

Appendix A.4 (Seki et al., 2020) CASP Appraisal



Influence of antihypertensive medications on the clinical parameters of anodized dental implants: a retrospective cohort study.  
 Paper for appraisal and reference:.....

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: A question can be 'focused' in terms of

- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

Comments:  
 The study clear aim - to investigate the effects of antihypertensive (AH) agents on the clinical parameters of anodized dental implants. This is beneficial as it could predict trends for peri implantitis or peri implant mucositis.

2. Was the cohort recruited in an acceptable way?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for selection bias which might compromise the generalisability of the findings:

- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

Comments:  
 Retrospective cohort study involving a single surgeon from a single centre over 15 years (2003-2018). The population was over 50 at the day of implant surgery which is largely indicative of the population who have dental implants placed and in line with other studies. Strict exclusion criteria which removed various confounders such as smoking, history of moderate / severe periodontal disease and any other systemic disease. By removing any other systemic disease is allows for data to be collected for only patients on AH medications which increases the validity of the study and reduced bias.

Is it worth continuing?

3. Was the exposure accurately measured to minimise bias?

Yes	X
Can't Tell	
No	

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments:

Clear definition of peri-implantitis and peri-implant mucositis. One examiner was used to measure all clinical parameters (probing depth, bleeding on probing, modified plaque index and marginal bone loss) which improves validity of the study. Subjects were divided into AH group vs healthy group. Subgroups included Calcium antagonists (CA), angiotensin ii receptor blockers (ARB), thiazide diuretics (TD) and combination (CA/ARB) (ARB/TD).

4. Was the outcome accurately measured to minimise bias?

Yes	X
Can't Tell	
No	

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
  - has a reliable system been established for detecting all the cases (for measuring disease occurrence)
    - were the measurement methods similar in the different groups
    - were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments:

A single examiner measured clinical parameters. Clinical parameters were measured objectively using the same measuring format for all cohorts. There is no mention of examiner blinding which could lead to bias but as measurements are objective, this is unlikely to be significant.



5. (a) Have the authors identified all important confounding factors?

Yes	x
Can't Tell	
No	

HINT:  
 • list the ones you think might be important, and ones the author missed

Comments:  
 Authors have excluded all sensible confounding factors from the study in the exclusion criteria - smokers, any other systemic disease and moderate to severe periodontal disease. Age, gender and implant site have also been discussed as confounding factors.

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes	x
Can't Tell	
No	

HINT:  
 • look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:  
 Authors have excluded all sensible confounding factors from the study in the exclusion criteria - smokers, any other systemic disease and moderate to severe periodontal disease. Age, gender and implant site have also been discussed as confounding factors.

6. (a) Was the follow up of subjects complete enough?

Yes	x
Can't Tell	
No	

HINT: Consider  
 • the good or bad effects should have had long enough to reveal themselves  
 • the persons that are lost to follow-up may have different outcomes than those available for assessment  
 • in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes	x
Can't Tell	
No	

Comments:

Subjects were followed up for 7 years and 1 month (mean). This is in line or better than other studies of this nature.

Section B: What are the results?

7. What are the results of this study?

HINT: Consider

- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments:

AH group are more susceptible to peri-implantitis. More of the AH implants were placed in the maxilla while a majority of the healthy group implants were placed in the mandible which was statistically significant. AH group implants had higher probing depths which were statistically significant. They also had worse clinical outcomes (bleeding, plaque and marginal bone loss) but these were not statistically significant.

8. How precise are the results?

HINT:

- look for the range of the confidence intervals, if given

Comments:

Small sample so the authors go into the results in detail which increase the accuracy of the results.



9. Do you believe the results?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- big effect is hard to ignore
  - can it be due to bias, chance or confounding
  - are the design and methods of this study sufficiently flawed to make the results unreliable
  - Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments:  
Results are believable owing to good study design and elimination of confounders. Small sample size though for AH group (13 patients) so results may differ if a larger sample is obtained.

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider whether
- a cohort study was the appropriate method to answer this question
  - the subjects covered in this study could be sufficiently different from your population to cause concern
  - your local setting is likely to differ much from that of the study
  - you can quantify the local benefits and harms

Comments:  
Results are believable but if a larger sample is obtained (such as 1000 patients) then results may differ.

11. Do the results of this study fit with other available evidence?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

Comments:  
Results similar to Alam-Eldein et al, 2017. Both studies found that dental implants in patients taking CCBs led to increased incidence of peri-implant disease.



12. What are the implications of this study for practice?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

**HINT: Consider**

- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
  - for certain questions, observational studies provide the only evidence
  - recommendations from observational studies are always stronger when supported by other evidence

Comments:

Study suggests that AH medications may lead to worse clinical parameters for patients taking these drugs. However, the study has a small sample size and results may change if the sample size increases. They also did not include all classes of AH medications (beta blockers were missing) which may effect results.

Appendix A.5 (Garcia-Denche et al., 2013) CASP Appraisal

**Study and citation:** Membranes over the lateral window in sinus augmentation procedures: a two-arm and split-mouth randomized clinical trials

**Section A: Is the basic study design valid for a randomised controlled trial?**

	Yes	No	Can't tell
<p><b>1. Did the study address a clearly focused research question?</b>                      CONSIDER:</p> <ul style="list-style-type: none"> <li>Was the study designed to assess the outcomes of an intervention?</li> <li>Is the research question 'focused' in terms of:                             <ul style="list-style-type: none"> <li>Population studied</li> <li>Intervention given</li> <li>Comparator chosen</li> <li>Outcomes measured?</li> </ul> </li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<p>This study evaluates whether or not, among other factors, membrane- coverage of anrostomy defects improves implant survival in sinus augmentation procedures. Single centre selected for the study.</p>			
<p><b>2. Was the assignment of participants to interventions randomised?</b>                      CONSIDER:</p> <ul style="list-style-type: none"> <li>How was randomisation carried out? Was the method appropriate?</li> <li>Was randomisation sufficient to eliminate systematic bias?</li> <li>Was the allocation sequence concealed from investigators and participants?</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<p>Subjects were blinded to group allocation. A single surgeon performed the sinus surgery and was unaware of group allocation until the final step of the surgery (placement of membrane or no membrane). A single prosthodontist was used for the restorative element of the RCT and they were blinded towards group allocation.</p>			
<p><b>3. Were all participants who entered the study accounted for at its conclusion?</b>                      CONSIDER:</p> <ul style="list-style-type: none"> <li>Were losses to follow-up and exclusions after randomisation accounted for?</li> <li>Were participants analysed in the study groups to which they were randomised (intention-to-treat analysis)?</li> <li>Was the study stopped early? If so, what was the reason?</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<p>Two patients were lost to follow up. Study was carried on to completion.</p>			

**Section B: Was the study methodologically sound?**

	Yes	No	Can't tell
<ul style="list-style-type: none"> <li>Were the participants 'blind' to intervention they were given?</li> <li>Were the investigators 'blind' to the intervention they were giving to participants?</li> <li>Were the people assessing/analysing outcome/s 'blinded'?</li> </ul>	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<p><b>5. Were the study groups similar at the start of the randomised controlled trial?</b>                      CONSIDER:</p> <ul style="list-style-type: none"> <li>Were the baseline characteristics of each study group (e.g. age, sex, socio-economic group) clearly set out?</li> <li>Were there any differences between the study groups that could affect the outcome/s?</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<p>Study groups had a similar split when compared to males/females, with membrane/without membrane and deferred placement/simultaneous placement.</p>			

<p><b>6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?</b></p> <p><i>CONSIDER:</i></p> <ul style="list-style-type: none"> <li>• Was there a clearly defined study protocol?</li> <li>• If any additional interventions were given (e.g. tests or treatments), were they similar between the study groups?</li> <li>• Were the follow-up intervals the same for each study group?</li> </ul>	<p>Yes <input checked="" type="checkbox"/></p>	<p>No <input type="checkbox"/></p>	<p>Can't tell <input type="checkbox"/></p>
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### Section C: What are the results?

<p><b>7. Were the effects of intervention reported comprehensively?</b></p> <p><i>CONSIDER:</i></p> <ul style="list-style-type: none"> <li>• Was a power calculation undertaken?</li> <li>• What outcomes were measured, and were they clearly specified?</li> <li>• How were the results expressed? For binary outcomes, were relative and absolute effects reported?</li> <li>• Were the results reported for each outcome in each study group at each follow-up interval?</li> <li>• Was there any missing or incomplete data?</li> <li>• Was there differential drop-out between the study groups that could affect the results?</li> <li>• Were potential sources of bias identified?</li> <li>• Which statistical tests were used?</li> <li>• Were p values reported?</li> </ul>	<p>Yes <input checked="" type="checkbox"/></p>	<p>No <input type="checkbox"/></p>	<p>Can't tell <input type="checkbox"/></p> <p>Outcomes were centred around dental implant survival. The study revealed that several factors led to a higher survival rate of dental implants, one of which was treatment for hypertension. Patients treated with antihypertensive (AH) medications had a survival rate of 89% which patients who were healthy had a survival rate of 87%. This data was statistically significant (<math>p=0.04</math>). A potential source of bias was the small number of patients included in the AH group (19) compared to the healthy group (85). It also doesn't state which drugs were included in the AH group.</p>
<p><b>8. Was the precision of the estimate of the intervention or treatment effect reported?</b></p> <p><i>CONSIDER:</i></p> <ul style="list-style-type: none"> <li>• Were confidence intervals (CIs) reported?</li> </ul>	<p>Yes <input checked="" type="checkbox"/></p>	<p>No <input type="checkbox"/></p>	<p>Can't tell <input type="checkbox"/></p> <p>Adjusted odds ratio for AH group 0.08 (0.01-0.94)</p>
<p><b>9. Do the benefits of the experimental intervention outweigh the harms and costs?</b></p> <p><i>CONSIDER:</i></p> <ul style="list-style-type: none"> <li>• What was the size of the intervention or treatment effect?</li> <li>• Were harms or unintended effects reported for each study group?</li> <li>• Was a cost-effectiveness analysis undertaken? (Cost-effectiveness analysis allows a comparison to be made between different interventions used in the care of the same condition or problem.)</li> </ul>	<p>Yes <input checked="" type="checkbox"/></p>	<p>No <input type="checkbox"/></p>	<p>Can't tell <input type="checkbox"/></p> <p>No harm came to patients. No augmentation material had to be regrafted and all patients were suitable for implant placement at the pre-selected recall time. Membrane coverage (the initial effect to be investigated) had no effect on implant survival. No cost-effect analysis was conducted although it can be assumed that not using a membrane will be a better financial option than using a membrane considering they have the same final outcome.</p>

**Section D: Will the results help locally?**

<p><b>10. Can the results be applied to your local population/in your context?</b></p> <p><i>CONSIDER:</i></p> <ul style="list-style-type: none"> <li>• Are the study participants similar to the people in your care?</li> <li>• Would any differences between your population and the study participants alter the outcomes reported in the study?</li> <li>• Are the outcomes important to your population?</li> <li>• Are there any outcomes you would have wanted information on that have not been studied or reported?</li> <li>• Are there any limitations of the study that would affect your decision?</li> </ul>	<p style="text-align: center;">Yes                      No                      Can't tell</p> <p style="text-align: center;"><input checked="" type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/></p> <p>Participants would be of a similar age to patients who usually get dental implants in a UK population (in this study, average age was 64.9 years). Participants would have to abide by inclusion and exclusion criteria applied in this study which may reduce numbers. Additional information is needed to increase the usefulness of the study. Information such as class of AH medication, dosing regimen and time spent on the drug would increase its validity. Increasing the sample size would also achieve this effect. Participants were followed up for 12 months and a longer follow up time would be useful to assess try survival outcomes which would be more reflective of real life.</p>
<p><b>11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?</b></p> <p><i>CONSIDER:</i></p> <ul style="list-style-type: none"> <li>• What resources are needed to introduce this intervention taking into account time, finances, and skills development or training needs?</li> <li>• Are you able to disinvest resources in one or more existing interventions in order to be able to re-invest in the new intervention?</li> </ul>	<p style="text-align: center;">Yes                      No                      Can't tell</p> <p style="text-align: center;"><input type="checkbox"/>                      <input type="checkbox"/>                      <input checked="" type="checkbox"/></p> <p>This study was primarily assessing the effect of placing a membrane over a dental implant during sinus augmentation. As such, the effect of AH medications increasing the survival outcomes of dental implants in these regions was a secondary finding. In future, a larger sample size of AH users is required. AH users would be subdivided by their class of drugs e.g. beta blockers, calcium channel blockers etc. for more detailed information of the effect of each class on dental implant survival.</p>

**APPRAISAL SUMMARY:** Record key points from your critical appraisal in this box. What is your conclusion about the paper? Would you use it to change your practice or to recommend changes to care/interventions used by your organisation? Could you judiciously implement this intervention without delay?

Ultimately, a larger sample size of AH users is required to increase the validity of the study. Using a multicentre RCT would further increase the validity as would subdividing AH users by their class of drug. This paper lacks the necessary detail for its results to be implemented and it also raises a question of would it be possible to implement the results. It is likely the negative effects of medicating patients of good health on AH medications would lead to systemically and prolonged hypotension would outweigh the positive effects of having better survival outcomes for implants placed during maxillary sinus augmentation.

Appendix A.6 (Malm et al., 2021) CASP Appraisal



Paper for appraisal and reference:

Section A: Are the results of the trial valid?

1. Did the study address a clearly focused issue?

Yes	X
Can't Tell	
No	

HINT: An issue can be 'focused' in terms of

- the population studied
- Whether the study tried to detect a beneficial or harmful effect
- the risk factors studied

Comments:

The aim of the study was to identify possible risk factors which may lead to early dental implant failure. Early was defined as within the first year of function. Various risk factors were investigated included age, gender, smoking status, systemic disease etc.

2. Did the authors use an appropriate method to answer their question?

Yes	X
Can't Tell	
No	

HINT: Consider

- Is a case control study an appropriate way of answering the question under the circumstances
- Did it address the study question

Comments:

A case control study is appropriate for this type of study however, it cannot produce a causal link due to the nature of the study. A prospective cohort study may be more appropriate involving patients treated with antihypertensive (AH) medications and a control group. If these patients were followed up for several years and cause of failure identified, this would be more beneficial. A prospective cohort would involve a longer follow up and additional time and resources which the authors may not have.



Is it worth continuing?

3. Were the cases recruited in an acceptable way?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

Comments:

Retrospective data obtained from a single centre. The study has a valid sample size of 816 participants which is evenly split between those who experienced early failure and those with no failure (control group).

HINT: We are looking for selection bias which might compromise validity of the findings

- are the cases defined precisely
- were the cases representative of a defined population (geographically and/or temporally)
- was there an established reliable system for selecting all the cases
  - are they incident or prevalent
- is there something special about the cases
  - is the time frame of the study relevant to disease/exposure
- was there a sufficient number of cases selected
- was there a power calculation

4. Were the controls selected in an acceptable way?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

Comments:

Control group did not have early failure. All patients were edentulous at the time of implant placement.

HINT: We are looking for selection bias which might compromise the generalisability of the findings

- were the controls representative of the defined population (geographically and/or temporally)
- was there something special about the controls
- was the non-response high, could non-respondents be different in any way
  - are they matched, population based or randomly selected
- was there a sufficient number of controls selected



5. Was the exposure accurately measured to minimise bias?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

HINT: We are looking for measurement, recall or classification bias

- was the exposure clearly defined and accurately measured
- did the authors use subjective or objective measurements
- do the measures truly reflect what they are supposed to measure (have they been validated)
- were the measurement methods similar in the cases and controls
- did the study incorporate blinding where feasible
- is the temporal relation correct (does the exposure of interest precede the outcome)

Comments:

No discussion regarding blinding of researchers.

6. (a) Aside from the experimental intervention, were the groups treated equally?

HINT: List the ones you think might be important, that the author may have missed

- genetic
- environmental
- socio-economic

List:

Groups were treated equally.

6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input checked="" type="checkbox"/>

- HINT: Look for
- restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:

No discussion regarding if all patients had the same make and model of implant placed, implant length and diameter or attached final prosthesis. A vast majority of implants were placed pre 2003. It would be important to assess the surgical protocols during this time frame to see if any differences have occurred as this could affect survival outcomes.

Section B: What are the results?

7. How large was the treatment effect?

Comments:

Results are conflicting. Having a circulatory disease was not associated with early implant failure not was treatment with a AH medication. However, having a systemic disease was associated with early failure.

- HINT: Consider
- what are the bottom line results
  - is the analysis appropriate to the design
  - how strong is the association between exposure and outcome (look at the odds ratio)
  - are the results adjusted for confounding, and might confounding still explain the association
  - has adjustment made a big difference to the OR

8. How precise was the estimate of the treatment effect?

Comments:

No discussion of what AH medications were investigated, dosing regime or time on the medication. There is also no discussion if the patient is on a single Ah medication or multiple or is there are other medical issues that may be relevant i.e. medicated on IV bisphosphonates, uncontrolled diabetes, periodontal disease.

- HINT: Consider
- size of the p-value
  - size of the confidence intervals
  - have the authors considered all the important variables
  - how was the effect of subjects refusing to participate evaluated



9. Do you believe the results?

Yes	X
No	

- HINT: Consider
- big effect is hard to ignore!
  - Can it be due to chance, bias, or confounding
  - are the design and methods of this study sufficiently flawed to make the results unreliable
  - consider Bradford Hills criteria (e.g. time sequence, does-response gradient, strength, biological plausibility)

Comments:  
Results are plausible but lack detail regarding which AH medications were investigated

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	X
Can't Tell	
No	

- HINT: Consider whether
- the subjects covered in the study could be sufficiently different from your population to cause concern
  - your local setting is likely to differ much from that of the study
  - can you quantify the local benefits and harms

Comments:  
Participants recruited in the study are of a similar age to adults in the UK who require treatment with dental implants. This study is investigating early failure in patients who were edentulous at the time of treatment and they may be prone to other systemic issues which were not addressed in the study i.e. xerostomia due to polypharmacy.

11. Do the results of this study fit with other available evidence?

Yes	
Can't Tell	X
No	

- HINT: Consider
- all the available evidence from RCT's Systematic Reviews, Cohort Studies, and Case Control Studies as well, for consistency

Comments:  
No other case control studies of this nature exist but it reflects results in some cohort studies which would suggest AH medications do not lead to early implant failure and even increase survival outcomes.

Appendix A.7 (Alam-Eldein et al., 2017) CASP Appraisal



Effect of calcium-channel blockers on clinical outcomes of implant retained overdenture in hypertensive patients

Paper for appraisal and reference:.....

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes	<b>x</b>
Can't Tell	
No	

**HINT:** A question can be 'focused' in terms of

- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

Comments:

This study compared the effects of Calcium channel-blocking agents (Amlodipine) and angiotensin receptor blockers (Valsartan) on dental implants retaining overdentures in hypertensive patients clinically and radiographically after two years of function.

2. Was the cohort recruited in an acceptable way?

Yes	
Can't Tell	<b>x</b>
No	

**HINT:** Look for selection bias which might compromise the generalisability of the findings:

- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

Comments:

Cohort consisted of 20 edentulous males of an average age of 50 which is only representative of a very small sample of any population. No mention of how the cohort was recruited.

Is it worth continuing?



3. Was the exposure accurately measured to minimise bias?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments:

Subjects were randomly divided into two groups depending on which hypertensive medication they have been medicated on - Amlodipine vs Valsartan. Participants had been on the drugs for an equal amount of time. Patients had the same length and diameter of implant placed in the same position via the same surgical approach. This was restored with the same prosthesis.

4. Was the outcome accurately measured to minimise bias?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
  - has a reliable system been established for detecting all the cases (for measuring disease occurrence)
  - were the measurement methods similar in the different groups
  - were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments:

Participants had the same outcome measures assessed - plaque control index, gingival index, probing depth, stability, marginal bone loss via radiographs. There is no discussion on who performed these investigations or if they were blinded to the groups.



5. (a) Have the authors identified all important confounding factors?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input checked="" type="checkbox"/>

HINT:  
 • list the ones you think might be important, and ones the author missed

Comments:  
 Discussion laboratory investigations to rule out systemic disease but no mention of what diseases they were trying to rule out or how they came to this conclusion. No discussion of smoking status.

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input checked="" type="checkbox"/>

HINT:  
 • look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:  
 All patients are supposedly medically well apart from their hypertension, age of a similar age and of the same gender. Confounding factors to do with the implants are limited due to the same implants being placed in the same position. No mention of smoking status which may be a confounding factor which was not discussed

6. (a) Was the follow up of subjects complete enough?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider  
 • the good or bad effects should have had long enough to reveal themselves  
 • the persons that are lost to follow-up may have different outcomes than those available for assessment  
 • in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

Comments:

No mention if any participants were lost to follow up. Participants were followed up for 2 years which is in line with other studies of this nature

Section B: What are the results?

7. What are the results of this study?

HINT: Consider

- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments:

Patients medicated on amlodipine had worse clinical parameters (increased plaque, increased bleeding, greater probing depths, less stable and greater bone loss) than those treated with Valsartan. This was not statistically significant.

8. How precise are the results?

HINT:

- look for the range of the confidence intervals, if given

Comments:

Results are accurate owing to small range.



9. Do you believe the results?

Yes	x
Can't Tell	
No	

- HINT: Consider
- big effect is hard to ignore
  - can it be due to bias, chance or confounding
  - are the design and methods of this study sufficiently flawed to make the results unreliable
  - Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments:  
Results are plausible and design of study is acceptable.

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	x
Can't Tell	
No	

- HINT: Consider whether
- a cohort study was the appropriate method to answer this question
  - the subjects covered in this study could be sufficiently different from your population to cause concern
  - your local setting is likely to differ much from that of the study
  - you can quantify the local benefits and harms

Comments:  
Results can be applied to a small subset of a population consisting of edentulous male adults over the age of 50 with hypertension who are medicated on either amlodipine or valsartan.

11. Do the results of this study fit with other available evidence?

Yes	
Can't Tell	x
No	

Comments:  
No other papers have tried to compare the clinical parameters of various antihypertensive medications.

12. What are the implications of this study for practice?

Yes	X
Can't Tell	
No	

- HINT: Consider**
- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
    - for certain questions, observational studies provide the only evidence
    - recommendations from observational studies are always stronger when supported by other evidence

**Comments:**

Increased awareness of the effects of dihydropyridine calcium channel blockers on gingival health as this may lead to gingival overgrowth and reduced outcomes. However, a larger sample size is needed to increase validity and to include a broader range of participant.

**References**

1. Steele, J.G.; Treasure, E.T.; O'Sullivan, I.; Morris, J.; Murray, J.J. Adult Dental Health Survey 2009: Transformations in British oral health 1968–2009. *Br. Dent. J.* **2012**, *213*, 523–527. [[CrossRef](#)] [[PubMed](#)]
2. Shah, R.J.; Diwan, F.J.; Diwan, M.J.; Chauhan, V.J.; Agrawal, H.S.; Patel, G.C. A study of the emotional effects of tooth loss in an edentulous Gujarati population and its association with depression. *J. Indian Prosthodont. Soc.* **2015**, *15*, 237–243. [[CrossRef](#)] [[PubMed](#)]
3. Matsuyama, Y.; Jürges, H.; Dewey, M.; Listl, S. Causal effect of tooth loss on depression: Evidence from a population-wide natural experiment in the USA. *Epidemiol. Psychiatr. Sci.* **2021**, *30*, e38. [[CrossRef](#)] [[PubMed](#)]
4. Bornstein, M.M.; Halbritter, S.; Harnisch, H.; Weber, H.-P.; Buser, D. A retrospective analysis of patients referred for implant placement to a specialty clinic: Indications, surgical procedures, and early failures. *Int. J. Oral Maxillofac. Implant.* **2008**, *23*, 1109–1116.
5. Sato, Y.; Kitagawa, N.; Isobe, A. Current Consensus of Dental Implants in the Elderly—What Are the Limitations? Current Oral Health Reports. *Int. J. Oral Maxillofac. Implant.* **2020**, *7*, 321–326.
6. Schimmel, M.; Müller, F.; Suter, V.; Buser, D. Implants for elderly patients. *Periodontology* **2017**, *73*, 228–240. [[CrossRef](#)] [[PubMed](#)]
7. Ellefsen, B.S.; Morse, D.E.; Waldemar, G.; Holm-Pedersen, P. Indicators for root caries in Danish persons with recently diagnosed Alzheimer's disease. *Gerodontology* **2012**, *29*, 194–202. [[CrossRef](#)] [[PubMed](#)]
8. Compton, S.M.; Clark, D.; Chan, S.; Kuc, I.; Wubie, B.A.; Levin, L. Dental Implants in the Elderly Population: A Long-Term Follow-up. *Int. J. Oral Maxillofac. Implant.* **2017**, *32*, 164–170. [[CrossRef](#)] [[PubMed](#)]
9. Martimbianco, A.L.C.; Prosdociami, F.C.; Anauate-Netto, C.; dos Santos, E.M.; Mendes, G.D.; Fragoso, Y.D. Evidence-Based Recommendations for the Oral Health of Patients with Parkinson's Disease. *Neurol. Ther.* **2021**, *10*, 391–400. [[CrossRef](#)] [[PubMed](#)]
10. Zenthöfer, A.; Schröder, J.; Cabrera, T.; Rammelsberg, P.; Hassel, A.J. Comparison of oral health among older people with and without dementia. *Community Dent. Health* **2014**, *31*, 27–31. [[PubMed](#)]
11. Kaufman, D.W.; Kelly, J.P.; Rosenberg, L.; Anderson, T.E.; Mitchell, A.A. Recent Patterns of Medication Use in the Ambulatory Adult Population of the United States The Slone Survey. *JAMA* **2002**, *287*, 337–344. [[CrossRef](#)] [[PubMed](#)]
12. Wu, X.; Al-Abedalla, K.; Abi-Nader, S.; Daniel, N.G.; Nicolau, B.; Tamimi, F. Proton Pump Inhibitors and the Risk of Osseointegrated Dental Implant Failure: A Cohort Study. *Clin. Implant. Dent. Relat. Res.* **2016**, *19*, 222–232. [[CrossRef](#)] [[PubMed](#)]

13. Altay, M.A.; Sindel, A.; Ozalp, O.; Yildirimyan, N.; Kocabalkan, B. Proton pump inhibitor intake negatively affects the osseointegration of dental implants: A retrospective study. *J. Korean Assoc. Oral Maxillofac. Surg.* **2019**, *45*, 135–140. [[CrossRef](#)] [[PubMed](#)]
14. Wu, X.; Al-Abedalla, K.; Rastikerdar, E.; Abi Nader, S.; Daniel, N.G.; Nicolau, B.; Tamimi, F. Selective serotonin reuptake inhibitors and the risk of osseointegrated implant failure: A cohort study. *J. Dent. Res.* **2014**, *93*, 1054–1061. [[CrossRef](#)] [[PubMed](#)]
15. Carr, A.B.; Gonzalez, R.L.V.; Jia, L.; Lohse, C.M. Relationship between Selective Serotonin Reuptake Inhibitors and Risk of Dental Implant Failure. *J. Prosthodont.* **2019**, *28*, 252–257. [[CrossRef](#)] [[PubMed](#)]
16. Chappuis, V.; Avila-Ortiz, G.; Araújo, M.G.; Monje, A. Medication-related dental implant failure: Systematic review and meta-analysis. *Clin. Oral Implant. Res.* **2018**, *29*, 55–68. [[CrossRef](#)]
17. Wu, X.; Al-Abedalla, K.; Eimar, H.; Madathil, S.A.; Abi-Nader, S.; Daniel, N.G.; Nicolau, B.; Tamimi, F. Antihypertensive Medications and the Survival Rate of Osseointegrated Dental Implants: A Cohort Study. *Clin. Implant. Dent. Relat. Res.* **2016**, *18*, 1171–1182. [[CrossRef](#)]
18. Scully, C. *Medical Problems in Dentistry*; Churchill Livingstone/Elsevier: Edinburgh, UK, 2014; pp. 111–113.
19. Rejnmark, L.; Vestergaard, P.; Mosekilde, L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: A nationwide case-control study. *J. Hypertens.* **2006**, *24*, 581–589. [[CrossRef](#)] [[PubMed](#)]
20. Takeda, S.; Elefteriou, F.; Lévassieur, R.; Liu, X.; Zhao, L.; Parker, K.L.; Armstrong, D.; Ducy, P.; Karsenty, G. Leptin regulates bone formation via the sympathetic nervous system. *Cell* **2002**, *111*, 305–317. [[CrossRef](#)] [[PubMed](#)]
21. Togari, A.; Arai, M. Pharmacological topics of bone metabolism: The physiological function of the sympathetic nervous system in modulating bone resorption. *J. Pharmacol. Sci.* **2008**, *106*, 542–546. [[CrossRef](#)] [[PubMed](#)]
22. Albrektsson, T.; Zarb, G.; Worthington, P.; Eriksson, A.R. The long-term efficacy of currently used dental implants: A review and proposed criteria of success. *Int. J. Oral. Maxillofac. Implant.* **1986**, *1*, 11–25.
23. Javed, F.; Ahmed, H.B.; Crespi, R.; Romanos, G.E. Role of primary stability for successful osseointegration of dental implants: Factors of influence and evaluation. *Interv. Med. Appl. Sci.* **2013**, *5*, 162–167. [[CrossRef](#)] [[PubMed](#)]
24. Buser, D.; Weber, H.P.; Lang, N.P. Tissue integration of non-submerged implants. 1-year results of a prospective study with 100 ITI hollow-cylinder and hollow-screw implants. *Clin. Oral. Implant. Res.* **1990**, *1*, 33–40. [[CrossRef](#)] [[PubMed](#)]
25. Lang, N.P.; Jepsen, S.; Working, G. Implant surfaces and design (Working Group 4). *Clin. Oral. Implant. Res.* **2009**, *20* (Suppl. S4), 228–231. [[CrossRef](#)] [[PubMed](#)]
26. Shalabi, M.M.; Gortemaker, A.; Van't Hof, M.A.; Jansen, J.A.; Creugers, N.H. Implant surface roughness and bone healing: A systematic review. *J. Dent. Res.* **2006**, *85*, 496–500. [[CrossRef](#)] [[PubMed](#)]
27. Saravi, B.; Vollmer, A.; Lang, G.; Adolphs, N.; Li, Z.; Giers, V.; Stoll, P. Impact of renin-angiotensin system inhibitors and beta-blockers on dental implant stability. *Int. J. Implant. Dent.* **2021**, *7*, 31. [[CrossRef](#)]
28. Seki, K.; Hasuike, A.; Iwano, Y.; Hagiwara, Y. Influence of antihypertensive medications on the clinical parameters of anodized dental implants: A retrospective cohort study. *Int. J. Implant. Dent.* **2020**, *6*, 32. [[CrossRef](#)] [[PubMed](#)]
29. Garcia-Denche, J.T.; Wu, X.; Martinez, P.P.; Eimar, H.; Ikbali, D.J.; Hernandez, G.; Lopez-Cabarcos, E.; Fernandez-Tresguerres, I.; Tamimi, F. Membranes over the lateral window in sinus augmentation procedures: A two-arm and split-mouth randomized clinical trials. *J. Clin. Periodontol.* **2013**, *40*, 1043–1051. [[CrossRef](#)] [[PubMed](#)]
30. Alam-Eldein, A.M.; Mabrouk, E.A. Effect of calcium channel-blockers on clinical outcomes of implant retained overdenture in hypertensive patients. *Egypt. Dent. J.* **2017**, *63*, 949–961. [[CrossRef](#)]
31. Malm, M.O.; Jemt, T.; Stenport, V.F. Patient factors related to early implant failures in the edentulous jaw: A large retrospective case-control study. *Clin. Implant. Dent. Relat. Res.* **2021**, *23*, 466–476. [[CrossRef](#)] [[PubMed](#)]
32. Barikani, H.; Rashtak, S.; Akbari, S.; Badri, S.; Daneshparvar, N.; Rokn, A. The effect of implant length and diameter on the primary stability in different bone types. *J. Dent.* **2013**, *10*, 449–455.
33. Folkman, M.; Becker, A.; Meinster, I.; Masri, M.; Ormianer, Z. Comparison of bone-to-implant contact and bone volume around implants placed with or without site preparation: A histomorphometric study in rabbits. *Sci. Rep.* **2020**, *10*, 12446. [[CrossRef](#)] [[PubMed](#)]
34. Jung, B.A.; Yildizhan, F.; Wehrbein, H. Bone-to-implant contact of orthodontic implants in humans—A histomorphometric investigation. *Eur. J. Orthod.* **2008**, *30*, 552–557. [[CrossRef](#)] [[PubMed](#)]
35. Liñares, A.; Mardas, N.; Dard, M.; Donos, N. Effect of immediate or delayed loading following immediate placement of implants with a modified surface. *Clin. Oral Implant. Res.* **2011**, *22*, 38–46. [[CrossRef](#)] [[PubMed](#)]
36. Vollmer, A.; Saravi, B.; Lang, G.; Adolphs, N.; Hazard, D.; Giers, V.; Stoll, P. Factors Influencing Primary and Secondary Implant Stability—A Retrospective Cohort Study with 582 Implants in 272 Patients. *Appl. Sci.* **2020**, *10*, 8084. [[CrossRef](#)]
37. Sachdeva, A.; Dhawan, P.; Sindwani, S. Assessment of Implant Stability: Methods and Recent Advances. *Br. J. Med. Med. Res.* **2016**, *12*, 1–10. [[CrossRef](#)] [[PubMed](#)]
38. Pagliani, L.; Sennerby, L.; Petersson, A.; Verrocchi, D.; Volpe, S.; Andersson, P. The relationship between resonance frequency analysis (RFA) and lateral displacement of dental implants: An in vitro study. *J. Oral Rehabil.* **2013**, *40*, 221–227. [[CrossRef](#)] [[PubMed](#)]
39. Makary, C.; Rebaudi, A.; Sammartino, G.; Naaman, N. Implant primary stability determined by resonance frequency analysis: Correlation with insertion torque, histologic bone volume, and torsional stability at 6 weeks. *Implant Dent.* **2012**, *21*, 474–480. [[CrossRef](#)]

40. Esposito, M.; Hirsch, J.M.; Lekholm, U.; Thomsen, P. Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology. *Eur. J. Oral Sci.* **1998**, *106*, 527–551. [[CrossRef](#)] [[PubMed](#)]
41. Lioubavina-Hack, N.; Lang, N.P.; Karring, T. Significance of primary stability for osseointegration of dental implants. *Clin. Oral Implant. Res.* **2006**, *17*, 244–250. [[CrossRef](#)] [[PubMed](#)]
42. Busenlechner, D.; Fürhauser, R.; Haas, R.; Watzek, G.; Mailath, G.; Pommer, B. Long-term implant success at the Academy for Oral Implantology: 8-year follow-up and risk factor analysis. *J. Periodontal Implant. Sci.* **2014**, *44*, 102–108. [[CrossRef](#)] [[PubMed](#)]
43. Krebs, M.; Schmenger, K.; Neumann, K.; Weigl, P.; Moser, W.; Nentwig, G.-H. Long-Term Evaluation of ANKYLOS® Dental Implants, Part I: 20-Year Life Table Analysis of a Longitudinal Study of More Than 12,500 Implants. *Clin. Implant. Dent. Relat. Res.* **2015**, *17* (Suppl. S1), e275–e286. [[CrossRef](#)] [[PubMed](#)]
44. Chrcanovic, B.R.; Kisch, J.; Albrektsson, T.; Wennerberg, A. Analysis of risk factors for cluster behavior of dental implant failures. *Clin. Implant. Dent. Relat. Res.* **2017**, *19*, 632–642. [[CrossRef](#)] [[PubMed](#)]
45. Bholra, M.; Neely, A.L.; Kolhatkar, S. Immediate implant placement: Clinical decisions, advantages, and disadvantages. *J. Prosthodont.* **2008**, *17*, 576–581. [[CrossRef](#)] [[PubMed](#)]
46. Cardaropoli, G.; Araújo, M.; Lindhe, J. Dynamics of bone tissue formation in tooth extraction sites. An experimental study in dogs. *J. Clin. Periodontol.* **2003**, *30*, 809–818. [[CrossRef](#)] [[PubMed](#)]
47. Cha, H.; Kim, A.; Nowzari, H.; Chang, H.; Ahn, K. Simultaneous sinus lift and implant installation: Prospective study of consecutive two hundred seventeen sinus lift and four hundred sixty-two implants. *Clin. Implant. Dent. Relat. Res.* **2014**, *16*, 337–347. [[CrossRef](#)] [[PubMed](#)]
48. Mishra, S.K.; Sonnahalli, N.K.; Chowdhary, R. Do antihypertensive medications have an effect on dental implants? A systematic review. *Oral Maxillofac. Surg.* **2023**, *online ahead of print*. [[CrossRef](#)] [[PubMed](#)]

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