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Calcineurin inhibitors in renal transplantation: Adverse effects

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Author: Matthew Jose

GUIDELINES

a. The use of tacrolimus is associated with a higher incidence of new onset, insulin-requiring diabetes mellitus compared with the use of cyclosporin postrenal transplant. This risk is greater with increasing tacrolimus-trough concentrations. (Level I evidence)

b. The use of cyclosporin is associated with a higher incidence of cosmetic side-effects and hyperlipidaemia compared with the use of tacrolimus postrenal transplant. (Level I evidence)

c. Gastrointestinal and neurological side-effects are more common in tacrolimus-treated recipients than in cyclosporin-treated recipients. (Level I evidence)

b. Both calcineurin inhibitors (CNI) produce a similar risk of infection and malignancy postrenal transplant. (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **The choice of CNI for an individual should be the one that will maximize allograft outcome and minimize adverse effects in the recipient.**
- **Many effects from CNI are concentration-related and in appropriate recipients, lowering the target concentration will reduce the effect of the drug (both immunological effects and adverse effects).**
- **Consideration must be given to the individual's demographics, comorbidities and concurrent medication when attempting to minimize adverse effects from medication post-transplant.**
- **Specific adverse effects such as hyperlipidaemia and gum hypertrophy may be controlled initially (by lipid-lowering agents or antibiotics respectively) without lowering the CNI target concentration.**

BACKGROUND

The introduction of CNI as immune-suppressants for kidney transplantation has dramatically improved both graft and patient survival. CNI (cyclosporin or tacrolimus) are now used as primary therapy in more than 90% of all kidney transplants in Australia.[1] This widespread use has led to the recognition of a significant number of clinically important adverse effects that have both immediate and long-term implications.

Published trials using CNI have mainly concentrated on transplant outcomes and have reported adverse effects far less frequently. In addition, transplant recipients are treated with a variety of medications and most are affected by medication-induced adverse effects whether CNI are used or not. Therefore, assigning a particular effect to a specific CNI alone in the context of transplantation should be viewed with caution.

The objectives of these guidelines are to:

a review the current evidence for CNI-specific adverse effects, and

b establish whether one CNI has a greater occurrence of a particular side-effect.

Recognized adverse effects of CNI include nephrotoxicity, hypertension, hyperlipidaemia, neurological, cosmetic and metabolic effects.

Post-transplant diabetes mellitus (PTDM) is reported to occur in 2–53% of all kidney transplants.[2] This broad figure is due mainly to the variety of definitions used in published trials and subsequently, international guidelines for the diagnosis of new-onset PTDM have been adopted.[3] These guidelines follow recommendations by the World Health Organization (WHO) and American Diabetes Association (ADA) and were developed with the aim of standardizing diagnosis both for clinical and research use. The recent development means that only studies designed and commencing post 2003 are likely to report on these standardized criteria. Prior to the publication of these guidelines, the most commonly used definition of PTDM was the post-transplant requirement for insulin (>30 days), but other definitions including the use of anti-diabetic medication, abnormal blood glucose level or oral glucose tolerance test have also been reported.[2]

Calcineurin inhibitors contribute to the development of new-onset PTDM by directly inhibiting insulin secretion from the pancreatic β-islet cell. This effect is both dose-dependant and reversible.[4] This is well demonstrated historically, with earlier studies using higher tacrolimus-trough concentrations (>15 ug/L) resulting in a greater incidence of PTDM.[5] The effect is amplified when CNI are used in

Correspondence: Dr Matthew Jose, Department of Nephrology, Royal Hobart Hospital, Hobart TAS 7000, Australia. Email: matthew.jose@ dhhs.tas.gov.au

conjunction with corticosteroids, which increase insulin resistance.

Many other factors also contribute to the incidence of PTDM including pretransplant glucose metabolism, family history, race, body mass index, steroid use and recipient age.[6,7]

SEARCH STRATEGY

Databases searched: Medline (1966 to July Week 3, 2004). MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for CNI and associated adverse effects. The results were then combined with the Cochrane highly sensitive search strategy for randomized controlled trials (RCT). The Cochrane Renal Group Specialized Register of RCT was also searched for relevant trials not indexed in Medline.
Date of searches: 27 July 2004.

WHAT IS THE EVIDENCE?

Level I evidence (systematic review)

Four systematic reviews reporting various adverse effects that occur post transplant have now been published.[2,8–10]

A Cochrane review comparing tacrolimus and cyclosporin as primary immunosuppression for kidney transplant recipients has recently been published.[10] The objectives of this meta-analysis were to summarize and compare the effects of the CNI – cyclosporin and tacrolimus – in renal transplantation. This review included 123 reports from 30 trials representing 4102 randomized renal transplant recipients. While the majority of trials in this review reported on graft outcome and episodes of acute rejection, fewer reported on adverse effects.

The reviewed trials covered a publication era of 1991–2003 and hence, none of the studies used 2 h monitoring of cyclosporin (C_2) and the tacrolimus-trough concentrations varied considerably over these 12 years. In addition, the 30 trials identified included six trials using the older oil-based cyclosporin (Sandimmune), 19 trials using the newer microemulsion formulation (Neoral) and five trials that did not specify formulation. Most trials were restricted to low-risk, unsensitized recipients with their first renal transplant. Adjunctive immunosuppression consisted of azathioprine in 16 trials, mycophenolate mofetil in eight trials, and either of these anti-proliferative agents in three three-arm trials. The remaining trials used sirolimus, mirzoribine or no anti-proliferative agent. Corticosteroid use and dose regimen was reported in 17 trials only. Thus, the heterogeneity of these trials lends some caution to the interpretation of the findings.

Malignancy and infection

No difference between cyclosporin and tacrolimus was identified for occurrence of malignancy or infection (bacterial, viral or total infection).

New-onset post-transplant diabetes mellitus

Across all included trials, tacrolimus-treated patients had a significantly increased risk at 6 months, 1 year and 3 years compared with cyclosporin-treated patients of new-onset PTDM (relative risk 1.86 at 1 year; 95% confidence interval (CI): 1.11, 3.09) and this risk increased with increasing tacrolimus-trough concentrations. The most consistent definition used in the trials was 'requirement for insulin therapy for >30 days' and was reported in 17 of the 30 trials at variable time points (3 months–5 years) post transplant. The studies reporting on this definition of diabetes were a heterogenous collection published from 1999 to 2002 and included Sandimmune cyclosporin, Neoral cyclosporin, azathioprine and mycophenolate mofetil-treated patients.

Hyperlipidaemia

Total cholesterol was reported in seven trials, with lower cholesterol seen in tacrolimus-treated patients at 6 months (mean difference –0.58 mmol/L; 95% CI: –0.77, –0.39). Triglyceride levels were reported in four trials with no difference between agents.

Cosmetic effects

Acne, hirsutism and gingival hyperplasia were all more common in cyclosporin-treated patients, while tacrolimus-treated recipients more frequently reported alopecia.

Other effects

Gastrointestinal effects (diarrhoea, vomiting and dyspepsia), neurological effects (tremor and headache) and hypomagnesaemia were more frequent in tacrolimus-treated recipients. The reported gastrointestinal effects were not due to concurrent mycophenolate mofetil use as most reporting trials used azathioprine. No difference in haematological adverse effects was found.

Summary and clinical implications

Webster *et al.*[10] concluded that for every 100 low-risk renal transplant recipients using tacrolimus instead of cyclosporin, they would avoid six episodes of acute rejection and one lost graft. For high-risk recipients, this number increases to preventing 17 acute rejection episodes and three grafts lost. However, using tacrolimus would render an extra five patients with new-onset diabetes mellitus (DM).

Other meta-analyses

A smaller systematic review of new-onset DM in kidney transplant recipients receiving CNI has also been published.[9] This study was partly funded by Novartis (maker of Sandimmune cyclosporin and Neoral cyclosporin) and included only seven prospective, randomized studies representing 1621 renal transplant recipients. Nevertheless,

the findings were consistent with Webster *et al.*,[10] with an average of 9.8% of tacrolimus-treated recipients and 2.7% of cyclosporin-treated recipients requiring insulin therapy (odds ratio 3.7, 1.10–6.46, $P < 0.00001$).

Montori *et al.*[2] conducted a systematic review of post-transplantation diabetes in solid organ transplants including heart, liver and kidney recipients. They found that the 12 month cumulative incidence of PTDM is lower in recent trials than three decades earlier and that immunosuppression explained 74% of the 12 month cumulative incidence. Tacrolimus had a higher incidence of PTDM compared with cyclosporin (relative risk 5.0; 95% CI: 2.2–11.5) when used in higher doses (>0.2 mg/kg per day), but not when used in lower doses (0.15–0.2 mg/kg per day). PTDM was associated with a small increase in mortality but is reported as improving over recent times.

An earlier meta-analysis consisting of four trials involving 1037 patients was published in 1999 by Knoll and Bell. Three of the included studies reported on the prevalence of DM at 1 year post transplant with tacrolimus-treated recipients again being more at risk (odds ratio 5.03, 2.04–12.36).

No other adverse effects were examined in these meta-analyses. These reviews also included a range of drugs, time periods, target concentrations and variable reporting of outcomes.

Level II evidence (individual trials)

Post-transplant diabetes mellitus

Most individual randomized trials are included in the most recent meta-analysis by Webster *et al.*[10] Trials included in these systematic reviews examining post transplant diabetes are included in Table 1 together with more recent studies.

Further RCT have not directly agreed with these findings and are limited by both trial design and reporting. The European Tacrolimus versus Cyclosporin Microemulsion Renal Transplantation Study Group[11] showed no difference in the use of anti-diabetic medication post kidney transplant over 2 years of follow up, but did not use ADA/WHO definitions of PTDM.

In a separate smaller study, African-American recipients ($n = 35$) of a kidney transplant were randomized to tacrolimus or cyclosporin. In tacrolimus-treated recipients, a lower serum creatinine and total cholesterol levels were seen at 1 year post transplant, but not at 3 and 5 years.[12]

Trials that are underway but without final published results include the DIRECT study (Diabetes Incidence after Renal Transplantation: Neoral C_2 monitoring *vs* Tacrolimus). This study uses recent ADA/WHO definitions of PTDM and has shown a 36% pooled incidence of impaired glucose metabolism, but final results are pending.[13]

Hirsutism and gum hypertrophy

Four comparative studies have reported hirsutism and five have reported on gum hypertrophy.[5,14–17] In all of these studies, the incidence of these cosmetic conditions was greater in patients taking cyclosporin (Table 2).

Hyperlipidaemia

Four studies all show a higher incidence or level of total cholesterol in patients taking cyclosporin for at least 6 months compared with tacrolimus (Table 3).[16–19] Conversion from cyclosporin to tacrolimus reduced both systolic and diastolic blood pressure together with serum lipids.[20]

Hypertension

Seven studies have reported on new-onset hypertension. Two of these show a greater incidence of hypertension in recipients treated with cyclosporin.[16,21] The remaining five studies show mixed results with no significant difference between the groups (Table 4).[5,21–24]

BK viral infection

Only one prospective randomized study examined viraemia and viruria post kidney transplant.[25] Although the study included 220 patients with 12 months of follow-up, no definite evidence of BK nephropathy was seen and the incidence of BK viraemia was similar in both cyclosporin and tacrolimus-treated patients.

Relationship to CNI target concentrations

Pascual *et al.*[26] reported improvement in systolic blood pressure, the number of antihypertensive medications used, serum triglyceride concentration and uric acid level when the dose of cyclosporin was reduced by 50%.[26] Similarly, targeting a lower 2 h concentration of cyclosporin also reduced the need for lipid-lowering therapy, suggesting that target concentrations are an important factor when adverse effects are concerned.

Level III evidence

Treatment of gum hypertrophy in cyclosporin-treated transplant recipients has been successful in occasional patients with oral metronidazole.[27] This effect may allow maintenance of cyclosporin doses as the antibiotic targets bacteria involved in the pathogenesis of chronic periodontal disease.

Withdrawal of CNI is increasingly common, but as yet, substitution with target of rapamycin (TOR) inhibitors has not shown a consistent improvement in cardiovascular risk profile or patient outcomes.[28] The use of TOR inhibitors in this study increased the incidence of impaired glucose tolerance.

SUMMARY OF THE EVIDENCE

Many factors determine both the therapeutic efficacy and adverse effects relating to a specific immunosuppressant. The published literature shows that adverse effects due to medication are common (Tables 1–7). To date, this literature reports that recipients treated with tacrolimus have an increased risk of developing post-transplant DM, but fewer hyperlipidemia and cosmetic side-effects than recipients treated with cyclosporin. This risk is related to therapeutic

drug exposure and becomes less with lower tacrolimus doses and trough concentrations.

The CNI of choice for an individual depends on local availability, the immunosuppression requirements for good allograft function and the individual risk profile of the recipient.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines:[39] Section IV: Long-term management of the transplant recipient:
A Careful long-term monitoring of graft recipients is mandatory to discover signs of immunosuppressive drug toxicity, in particular nephrotoxicity.
B In the case of a discrepancy between the drug dose and signs of toxicity, a thorough pharmacokinetic analysis should be performed.
C Cardiovascular, renal and metabolic risks and the risk of de novo malignancy must be considered in a long-term monitoring programme.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1 All randomized studies of CNI should adopt standard definitions of adverse effects and publish these together with graft outcomes.
2 Longer-term trials (greater than 6 or 12 months) should be designed to assess the effect of the difference between the CNI and impact on patient and graft outcome.

CONFLICT OF INTEREST

Matthew Jose has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Randomized controlled trials reporting on post-transplant diabetes mellitus

Author	Year	Inclusion	Intervention	*n*	Definition	Cyclosporin (%)	Tacrolimus (%)	Significance
Shapiro *et al.*[29]	1991	A	Cy-S *vs* Tac	57	>30 d Ins/1 yr	12.0	20.0	
Laskow *et al.*[30]	1995		Cy-S *vs* Tac	130	>30 d Ins/1 yr	5.0	24.0	
Vincenti *et al.*[31]	1996	A, B	Cy *vs* Tac	120	>30 d Ins/1 yr	5.0	25.0	
Mayer *et al.*[5]	1997	A, B	Cy-S *vs* Tac	448	>30 d Ins/1 yr	2.2	8.3	
Pirsch *et al.*[14]	1997	A, B	Cy-S *vs* Tac	412	>30 d Ins/1 yr	4.0	19.9	$P < 0.001$
Morris-Stiff *et al.*[32]	1998	B	Cy-M *vs* Tac	179	>30 d Ins/3 mo	2.2	0	P = NS
Raofi *et al.*[18]	1999		Cy-M *vs* Tac	35	>30 d Ins/1 yr	30.0	25.0	
Yang *et al.*[15]	1999		Cy-M *vs* Tac	60	Nil/6 mo	4.8	4.2	
Wang *et al.*[33]	2000		Cy-M *vs* Tac	57	>30 d Ins/1 yr	13.4	20.0	
Johnson *et al.*[34]	2000	B	Cy-M *vs* Tac	223	>30 d Rx/3 yr	6.5	27.8	$P = 0.002$
White *et al.*[35]	2000		Cy-M *vs* Tac	102	Nil/1 yr	8.0	4.0	
Busque *et al.*[36]	2001				>30 d Ins/6 mo	5.0	10.0	P = NS
Miller *et al.*[37]	2002		Cy-M *vs* Tac	53	>30 d Ins/1 yr	18.0	10.0	
Margreiter *et al.*[16]	2002		Cy-M *vs* Tac	560	>30 d Ins/1 yr	3.7	8.0	$P = 0.032$
Van Dujuhoven *et al.*[38]	2002	B	Cy *vs* Tac	23	>30 d Ins/6 mo	0	0	P = NS
Trompeter *et al.*[17]	2002		Cy-M *vs* Tac	204	>30 d Ins/1 yr	3.0	2.2	
Campos *et al.* [21]	2002		Cy-M *vs* Tac	166	Nil/1 yr	3.0	8.5	$P = 0.03$
Charpentier *et al.*[19]	2003		Cy-M *vs* Tac		NODM/6 mo	1.1	7.3	$P = 0.014$
Kim *et al.*[24]	2004		Cy *vs* Tac	87	NODM/6 mo	0	7.8	$P > 0.05$

Table 2 Randomized controlled trials reporting on hirsutism and gingival hyperplasia

Author	Year	Intervention	*n*	Gums (G)/ Hirsutism (H)	Cyclosporin (%)	Tacrolimus (%)	Significance
Mayer *et al.*[5]	1997	Cy-S *vs* Tac	448	Both	9.7 (H), 5.3 (G)	0 (H), 0 (G)	$P < 0.002$
Pirsch *et al.*[14]	1997	Cy-S *vs* Tac	412	Both	8.7 (H), 4.0 (G)	0.5 (H), 0.5 (G)	$P < 0.01$
Yang *et al.*[15]	1999	Cy-M *vs* Tac	60	G	6.7 (G)	0 (G)	$P < 0.01$
Margreiter *et al.*[16]	2002	Cy-M *vs* Tac	560	Both	4.4 (H), 4 (G)	0 (H), 0 (G)	$P < 0.002$
Trompeter *et al.*[17]	2002	Cy-M *vs* Tac	204	Both	7.5 (H), 5.3 (G)	0 (H), 0 (G)	$P = 0.023$

Table 3 Randomized controlled trials reporting on hypercholesterolaemia

Author	Year	Intervention	*n*	T.Chl	Cyclosporin	Tacrolimus	Significance
Raofi *et al.*[18]	1999	Cy-M *vs* Tac	35	12 mo	244 mg/dL mean	198 mg/dL	$P = 0.03$
Margreiter *et al.*[16]	2002	Cy-M *vs* Tac	560	6 mo	8.9% elevated Chl	2%	$P = 0.03$
Trompeter *et al.*[17]	2002	Cy-M *vs* Tac	204	6 mo	5.02 mmol/L mean	4.32 mmol/L	$P < 0.01$
Charpentier *et al.*[19]	2003	Cy-M *vs* Tac	370	6 mo	6.5% elevated Chl	2.7%	$P = 0.014$

Table 4 Randomized controlled trial reporting on post-transplant hypertension

Author	Year	Intervention	*n*	Cyclosporin (%)	Tacrolimus (%)	Significance
Mayer *et al.*[5]	1997	Cy-S *vs* Tac	448	73.0	70.0	P = NS
Pirsch *et al.*[14]	1997	Cy-S *vs* Tac	412	[illegible]	50.0	P = NS
Margreiter *et al.*[16]	2002	Cy-M *vs* Tac	560	23.2	15.7	$P = 0.032$
Trompeter *et al.*[17]	2002	Cy-M *vs* Tac	204	61.3	68.9	P = NS
Campos *et al.*[21]	2002	Cy-M *vs* Tac	[illegible]	24.0	11.0	$P = 0.003$
Charpentier *et al.*[19]	2003	Cy-M *vs* Tac	370	24.0	17.0	P = NS
Kim *et al.*[24]	2004	Cy-M *vs* Tac	87	59.6	48.7	P = NS

Table 5 Characteristics of included studies

Study ID (author, year)	*n*	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)
Busque *et al.*, 2001[36]	67	Randomized controlled clinical trial	6 renal centres, Canada	Kidney transplant recipients, cadaveric first transplant	Tacrolimus	Cyclosporin	6
Campos *et al.*, 2002[21]	166	Randomized controlled clinical trial	15 renal centres, Brazil	Kidney transplant recipients	Tacrolimus	Cyclosporin	12
Charpentier *et al.*, 2003[19]	555	Randomized controlled clinical trial	30 renal centres, Europe	Kidney transplant recipients	Tacrolimus	Cyclosporin	6
Johnson *et al.*, 2000[34]	223	Randomized controlled clinical trial	15 renal centres, North America	Kidney transplant recipients, cadaveric first transplant	Tacrolimus	Cyclosporin	3 years
Kim *et al.*, 2004[24]	87	Randomized controlled clinical trial	Single centre, Korea	First living donor transplant with no diabetes mellitus	Tacrolimus	Cyclosporin	12
Laskow *et al.*, 1995[30]	130	Randomized controlled clinical trial	5 renal centres, USA	Kidney transplant recipient	Tacrolimus	Cyclosporin	12
Margreiter *et al.*, 2002[16]	560	Randomized controlled clinical trial	50 renal centres, Europe	Kidney transplant recipients	Tacrolimus	Cyclosporin	3 years
Mayer *et al.*, 1997[5]	448	Randomized controlled clinical trial	15 renal clinics, Europe	Kidney transplant recipient, cadaveric	Tacrolimus	Cyclosporin	5 years

Table 5 *Continued*

Study ID (author, year)	*n*	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)
Miller *et al.*, 2002[37]	53	Randomized controlled clinical trial	USA	Kidney transplant recipient, cadaveric first transplant	Tacrolimus	Cyclosporin	12
Morris-Stiff *et al.*, 1998[32]	179	Randomized controlled clinical trial	Single centre, UK	Kidney transplant recipient, cadaveric	Tacrolimus	Cyclosporin	3 years
Pirsch *et al.*, 1997[14]	412	Randomized controlled clinical trial	19 renal clinics, USA	Kidney transplant recipient, cadaveric	Tacrolimus	Cyclosporin	5 years
Raofi *et al.*, 1999[18]	35	Randomized controlled clinical trial	Single centre, USA	African-American kidney transplant recipient, first transplant cadaveric	Tacrolimus	Cyclosporin	12
Shapiro *et al.*, 1991[29]	57	Randomized controlled clinical trial	Single centre, USA	Kidney transplant recipient, cadaveric first transplant	Tacrolimus	Cyclosporin	12
Trompeter *et al.*, 2002[17]	204	Randomized controlled clinical trial	18 renal centres, Europe	Paediatric kidney transplant recipients	Tacrolimus	Cyclosporin	6
Van Dujuhoven 2002[38]	23	Randomized controlled clinical trial	Single centre, the Netherlands	Kidney transplant recipient, cadaveric	Tacrolimus	Cyclosporin	6
Vincenti *et al.*, 1996[31]	120	Randomized controlled clinical trial	60 centres in 16 countries	Kidney transplant recipient	Tacrolimus	Cyclosporin	12
Wang *et al.*, 2000[33]	57	Randomized controlled clinical trial	Single centre, China	Kidney transplant recipient, cadaveric	Tacrolimus	Cyclosporin	12
White *et al.*, 2000[35]	102	Randomized controlled clinical trial	Single centre, UK	Kidney transplant recipients	Tacrolimus	Cyclosporin	12
Yang *et al.*, 1999[15]	60	Randomized controlled clinical trial	Single centre, USA	Kidney transplant recipient, first transplant	Tacrolimus	Cyclosporin	12

Table 6 Quality of randomized trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		Participants	Investigators	Outcome assessors		
Busque *et al.*, 2001[36]	Not specified	No	No	No	Unclear	Unclear
Campos *et al.*, 2002[21]	Not specified	No	No	No	No	1.0
Charpentier *et al.*, 2003[19]	Not specified	No	No	No	Yes	12.0
Johnson *et al.*, 2000[34]	Not specified	No	No	No	Yes	0.0
Kim *et al.*, 2004[24]	Not specified	No	No	No	Unclear	0.0
Laskow *et al.*, 1995[30]	Central	No	No	No	No	8.0
Margreiter *et al.*, 2002[16]	Central	No	No	No	No	23.0
Mayer *et al.*, 1997[5]	Not specified	No	No	No	Yes	0.0
Miller *et al.*, 2002[37]	Not specified	No	No	No	Yes	Unclear
Morris-Stiff *et al.*, 1998[32]	Not specified	No	No	No	Yes	0.0
Pirsch *et al.*, 1997[14]	Not specified	No	No	No	Yes	0.0
Raofi *et al.*, 1999[18]	Medical record number	No	No	No	Yes	Unclear
Shapiro *et al.*, 1991[29]	Not specified	No	No	No	No	Unclear

Table 6 *Continued*

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		Participants	Investigators	Outcome assessors		
Trompeter *et al.*, 2002[17]	Central	No	No	No	No	10.0
Van Dujuhoven 2002[38]	Sealed envelopes	No	No	No	No	Unclear
Vincenti *et al.*, 1996[31]	Not specified	No	No	No	Unclear	Unclear
Wang *et al.*, 2000[33]	Not specified	No	No	No	Yes	0.0
White *et al.*, 2000[35]	Not specified	No	No	No	Unclear	2.0
Yang *et al.*, 1999[15]	Not specified	No	No	No	Yes	0.0

Table 7 Results of dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (95% CI)	Risk difference (95% CI)
Busque *et al.*, 2001[36]	Diabetes mellitus >30 d insulin/6 mo sustained at 6 mo	3/46	0/21	3.28 (0.18, 60.73)	0.07 (–0.03, 0.16)
	Diabetes mellitus >30 d insulin/6 mo at 6 mo in previously non-diabetics	5/46	1/21	2.28 (0.28, 18.35)	0.06 (–0.07, 0.19)
Campos *et al.*, 2002[21]	Diabetes mellitus1 yr	5/822	2/76	2.32 (0.46, 11.59)	–0.02 (–0.06, 0.02)
	Diabetes mellitus1 yr in previously non-diabetic	2/82	3/76	3.09 (0.88, 10.80)	0.08 (0.00, 0.17)
	Hypertension	20/84	9/80	2.12(1.03, 4.37)	0.13 (0.01, 0.24)
Charpentier *et al.*, 2003[19]	Diabetes mellitus NODM/6 mo	27/371	2/184	6.70 (1.61, 27.85)	0.06 (0.03, 0.09)
	Hypercholesterolaemia	8/371	12/184	0.33 (0.14, 0.79)	0.06 (0.03, 0.09)
Johnson *et al.*, 2000[34]	Diabetes mellitus >30 d Rx/3 yr sustained at 3 yr	17/99	3/46	2.63 (0.81, 8.54)	–0.04 (–0.08, –0.01)
	Diabetes mellitus >30 d Rx/3 yr previously non-diabetic at 3 yr	17/99	3/46	2.63 (0.81, 8.54)	0.11(0.00, 0.21)
Kim *et al.*, 2004[24]	Diabetes mellitus NODM/6 mo	3/43	0/44	7.16 (0.38, 134.60)	0.07 (–0.02, 0.16)
	Hypercholesterolaemia	14/43	22/44	0.65 (0.39, 1.10)	–0.17 (–0.38, 0.03)
	Hypertension	22/44	28/44	0.80 (0.56, 1.16)	–0.12 (–0.33, 0.08)
Laskow *et al.*, 1995[30]	Diabetes mellitus 30 d insulin/1 yr sustained at 1 yr	12/67	1/20	3.58 (0.50, 25.89)	0.13 (0.00, 0.26)
	Diabetes mellitus 30 d insulin/1 yr at 1 yr in previously non-diabetics	17/67	1/20	5.07 (0.72, 35.81)	0.20 (0.06, 0.35)
Margreiter *et al.*, 2002[16]	Diabetes mellitus 30 d insulin/1 yr sustained at 1 yr	14/264	7/251	1.90 (0.78, 4.63)	0.03 (–0.01, 0.06)
	Diabetes mellitus 30 d insulin/1 yr at 1 yr in previously non-diabetics	19/264	16/251	1.13 (0.59, 2.15)	0.01 (–0.04, 0.05)
	Hirsuitism	0/286	12/271	0.04 (0.00, 0.64)	–0.04 (–0.07, –0.02)
	Gingival hyperplasia	0/286	11/271	0.04 (0.00, 0.70)	–0.04 (–0.06, –0.02)
	Hypercholesterolaemia	12/286	24/271	0.47 (0.24, 0.93)	–0.05 (–0.09, –0.01)
	Hypertension	45/286	63/271	0.68 (0.48, 0.96)	–0.08 (–0.14, –0.01)

Table 7 *Continued*

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (95% CI)	Risk difference (95% CI)
Mayer *et al.*, 1997[5]	Diabetes mellitus 30 d insulin/1 yr sustained at 1 yr	17/288	31/139	2.73 (0.82, 9.18)	–0.16 (–0.24, –0.09)
	Diabetes mellitus 30 d insulin/1 yr at 1 yr in previously non-diabetics	35/288	31/139	5.63 (1.76, 17.99)	–0.10 (–0.18, –0.02)
	Hirsuitism	0/303	14/145	0.0[illegible] (0.[illegible], 0.28)	–0.10 (–0.15, –0.05)
	Gingival hyperplasia	4/303	9/145	[illegible]1 (0.07, 0.6[illegible])	–0.05 (–0.09, –0.01)
	Hypertension	111/303	56/145	0.9[illegible] (0.74, 1.22)	–0.02 (–0.12, 0.08)
Miller *et al.*, 2002[37]	Diabetes mellitus 30 d insulin/1 yr at 1 yr	7/78	9/45	0.45 (1.[illegible]0, 11.78)	–0.11 (–0.24, 0.02)
Morris-Stiff *et al.*, 1998[32]	Diabetes mellitus 30 d insulin/1 yr	0/40	1/40	0.33 (0.01, 7.95)	–0.03 (–0.09, 0.04)
Pirsch *et al.*, 1997[14]	Diabetes mellitus 30 d insulin/1 yr at 5 yr sustained	20/151	6/151	3.33 (1.38, 8.07)	0.09 (0.03, 0.16)
	Diabetes mellitus 30 d insulin/1 yr at 5 yr previously non-diabetic	34/1[illegible]	71/151	4.86 (2.22, 10.61)	–0.25 (–0.35, –0.14)
	Hirsuitism	1/205	18/207	0.06 (0.01, 0.42)	–0.08 (–0.12, –0.04)
	Gingival hyperplasia	1/205	11/207	0.09 (0.01, 0.70)	–0.05 (–0.08, –0.02)
	Hypercholesterolaemia	[illegible]/205	30/207	0.54 (0.30, 0.96)	–0.07 (–0.13, –0.01)
	Hypertension	102/205	108/207	0.95 (0.79, 1.15)	–0.02 (–0.12, 0.07)
Raofi *et al.*, 1999[18]	Diabetes mellitus 30 d insulin/1 yr at 1 yr	3/10	4/16	1.20 (0.34, 4.28)	0.05 (–0.30, 0.40)
Shapiro *et al.*, 1991[29]	Diabetes mellitus 30 d insulin/1 yr sustained at 1 yr	2/20	1/15	1.50 (0.15, 15.04)	0.03 (–0.15, 0.22)
	Diabetes mellitus 30 d insulin/1 yr at 1 yr in previously non-diabetics	4/20	2/15	1.50 (0.32, 7.14)	0.07 (–0.18, 0.31)
Trompeter *et al.*, 2002[17]	Diabetes mellitus 30 d insulin/1 yr sustained at 6 mo	3/100	2/93	1.40 (0.24, 8.16)	0.01 (–0.04, 0.05)
	Hirsuitism	0/103	7/93	0.06 (0.00, 1.04)	–0.08 (–0.13, –0.02)
	Gingival hyperplasia	0/103	5/93	0.08 (0.00, 1.47)	–0.05 (–0.10, 0.00)
	Hypertension	71/103	57/93	1.12(0.91, 1.38)	0.08 (–0.06, 0.21)
Van Dujuhoven 2002[38]	Diabetes mellitus 30 d insulin/6 mo	0/11	0/12	Not estimable	0.00 (–0.15, 0.15)
Wang *et al.*, 2000[33]	Diabetes mellitus 30 d insulin/1 yr previously non-diabetics	5/25	4/32	1.60 (0.48, 5.35)	0.08 (–0.12, 0.27)
White *et al.*, 2000[35]	Diabetes mellitus nil/1 yr sustained at 1 yr	4/45	2/48	2.13 (0.41, 11.09)	0.05 (–0.05, 0.15)
	Diabetes mellitus nil/1 yr previously non-diabetics at 1 yr	4/45	2/48	2.13 (0.41, 11.09)	0.05 (–0.05, 0.15)
Yang *et al.*, 1999[15]	Diabetes mellitus nil/ 6 mo at 1 yr	1/24	1/21	0.88 (0.06, 13.14)	–0.01 (–0.13, 0.12)
	Gingival hyperplasia	0/30	2/30	0.20 (0.01, 4.00)	–0.07 (–0.17, 0.04)