Selective beta-1 blockers deteriorate glucose metabolism

A meta-analysis

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ABSTRACT

الأهداف: تجهيز مركب جديد من البيانات المتاحة وقياس أثر محصرات بيتا الإنتقائية على استقلاب الجلوكوز في المرضى الضغط والسكري باستخدام تقنية التحليل المجتمعة.

الطريقة: أجري بحث بقواعد البيانات المكتبة الالكترونية وقاعدة ميدبيس وميدلاين خلال الفترة من بداية يوليو حتى نهايته 2013م في المستشفى التابع لجامعة نانتشنغ، نانتشنغ، الصين. قمنا بجمع التجارب العشوائية المحكمة التي تشير إلى تأثير محصرات بيتا الإنتقائية المركزة على استقلاب الجلوكوز لدى مرضى السكر والضغط. تم فحص البيانات وتقيمها واستخراجها عن طريق باحثين مستقلين طبقاً لمعايير الاختيار وأجري تحليل باستخدام برنامج ريف مان 5.

النتائج: تم إدارج 7 دراسات شملت 1354 مريض. أظهرت الدراسة أنه عند المقارنة مع مجموعة الشاهد كانت محصرات بيتا الإنتقائية مرتبطة مع ارتفاع جلوكوز الدم (فرق المتوسط الموزون=0.21، الثقة 95%، فترة الثقة= 0.16-0.27، p<0.00001). وأظهرت النتائج عدم وجود اختلاف إحصائي في هيموجلوبين الجلوكوز (فرق المتوسط الموزون=0.13، الثقة 95%، فترة الثقة -.11، 0.37، p=0.28. انسولين السكر (فرق المتوسط الموزون=-1.13، الثقة 95%، فترة الثقة -4.27 ، 2.01، p=0.48 وزيادة الوزن (فرق المتوسط الموزون=1، الثقة 95%، فترة الثقة -1.08، 3.08، p=0.35.

خاتمة: ارتبطت محصرات بيتا الإنتقائية مع ارتفاع جلوكوز سكر الدم. ولا يجب استخدامها لمرضى الضغط والسكر.

Objectives: To provide an up-to-date synthesis of available data, and to quantify the effect of highly selective beta-1 blockers on glucose metabolism in patients with essential hypertension and type diabetes mellitus (T2DM) by using pooled analysis techniques.

Methods: Cochrane Library, PubMed, MEDLINE, and EMBASE databases were searched from inception to July 2013 in the Third Affiliated Hospital of Nanchang University, Nanchang, China. We collected randomized controlled trails reporting on the effect of highly selective beta-1 blockers on glucose metabolism in patients with hypertension and type 2 diabetes. Data was screened, evaluated, and extracted by 2 independent researchers according to the inclusion and exclusion criteria. Meta-analysis was conducted using RevMan5.0 software.

Results: Seven trials were enrolled in the meta-analysis including a total of 1354 patients. Meta-analysis results revealed that when compared with the control group, selective beta-1 blockers were associated with a higher fasting blood glucose (weighed mean difference: 0.21, 95% confidence interval [CI]: 0.16-0.27; p<0.00001). But results revealed no significant difference in glycosylated hemoglobin (weighed mean difference: 0.13, 95% CI: -0.11 to 0.37; p=0.28), fasting insulin (weighed mean difference: -1.13, 95% CI: -4.27 to 2.01; p=0.48), and gain in body weight (weighed mean difference: 1, 95% CI: -1.08 to 3.08; p=0.35).

Conclusion: Selective beta-1 blockers were associated with elevated fasting blood glucose. Thus, it should not be used for patients with essential hypertension and diabetes.

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Hypertensive diabetic individuals are at high risk for cardiovascular complications and this is a double risk factor for cardiovascular diseases. Hypertensive patients usually have insulin resistance, which leads to glucose, lipid, and other metabolic disorders, and in turn makes treatment of hypertension more complex.[1] There is substantial overlap between diabetes and hypertension. In the US population, evidence revealed that hypertension occurs in approximately 30% of patients with type 1 diabetes and in 50% to 80% of patients with type 2 diabetes,[2] evidence revealed that 58% of patients with diabetes had high blood pressure, and 44% of patients with hypertension had impaired glucose tolerance. According to the ACCOMPLISH (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension) trial,[3] a combination of a renin-angiotensin system blocker including angiotensin converting enzyme inhibitors (ACEI), angiotensin 2 receptor blockers (ARB) as well as a calcium channel blocker (CCB) should probably be the first choice in patients with diabetes and hypertension. However, the efficacy of beta blockers on hypertensive diabetic patients is unclear. There has been concern over adverse effects of beta blockers in diabetic patients, since it decreases insulin sensitivity and impairs glucose tolerance.[4,5] This has led to blockers being relegated to fourth-line treatment of essential hypertension.[6] But the highly selective beta-1 blockers such as nebivolol have been shown to be favorable in short term (6 months) treatment.[7] There are inconsistencies in conclusions between various studies.[8-14] Therefore, a systematic review is required to provide an up-to-date synthesis of available data. In this study, we intended to quantify the effect of highly selective beta-1 blockers on glucose metabolism in patients with essential hypertension and type 2 diabetes mellitus (T2DM) by using pooled analysis techniques.

Methods. The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, PubMed, MEDLINE, and EMBASE databases were searched from inception to July 2013 in the Third Affiliated Hospital of Nanchang University, Nanchang, China using the keywords of hypertension, T2DM, beta-1-blocker, metoprolol, atenolol, and bisoprolol. The bibliographies of identified studies were checked. The Medline query was limited to studies involving human subjects, randomized controlled trials, and/or meta-analyses. No language restrictions were applied.

Selection criteria. A systematic review of the literature with meta-analysis was needed to identify all clinical trials evaluating the effect of beta blockers on glucose metabolism including fasting blood glucose (FBG), 2 hours postprandial blood glucose (2hPBG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS), 2 hours postprandial insulin (2hPINS), C peptide levels, body mass index (BMI), heart rate (HR), insulin resistance index (HOMA-IR), and insulin sensitivity index (ISI). Eligible studies had to be randomized controlled trials. The test group are highly selective beta-1-blockers such as metoprolol, atenolol, and bisoprolol. Other interventions in the control group must be consistent with the test group. All patients with essential hypertension and T2DM fulfilled the diagnostic criteria. The diagnostic criteria of hypertension was a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.[15] The diagnostic criteria of T2DM was a fasting plasma glucose ≥7.0 mmol/L or 2-hour postprandial plasma glucose ≥11.1 mmol/L.[16] Additional inclusion criteria included: patients <18 years, treatment for >30 days, and follow-up ≥1 month. There was no limitation on race, gender, and disease duration. Pregnancy-induced hypertension, malignant hypertension, rapidly progressive hypertension, type 1 diabetes, drug-induced diabetes, and other special types such as maturity onset diabetes mellitus in young, or Rabson-Mendenhall syndrome were excluded. Trials involving patients with severe complications were excluded.

Data abstraction. Two investigators screened the literature, and extracted the data independently. Their differences were resolved through discussions with the third parties. Abstracted data included eligibility criteria, baseline characteristics, study design (including treatment and control arms), follow-up, and outcomes. Outcomes were analyzed according to intention-to-treat. All included studies were randomized controlled trials. The quality of the included studies were evaluated according to allocation concealment (blinded randomization), lost to follow-up and drop-out rates, baseline studies, diagnostic criteria, controlling for confounding according to the systematic reviews of the Cochrane Collaboration Handbook 5.0. The study selection process is shown in **Figure 1**.

Statistical analysis. We used Review Manager 5.0 software (International Cochrane Collaboration) to perform data analysis. The pooled mean difference (MD) and its corresponding 95% confidence intervals (CI) were calculated from each model to assess the clinical outcomes. Chi-square tests were performed to assess statistical heterogeneity. Inconsistency (I^2) values of 25 was considered as evidence of low, 50 as moderate, and 75% as high heterogeneity.[17] If the *p*-value of

heterogeneity tests was >0.1 or inconsistency (I^2) <50%, the fixed effect analysis of the Mantel–Haenszel model was chosen to perform the meta-analysis. Otherwise, the random effect model based on the DerSimonian and Laird estimator was used.[18] A funnel plot was generated to evaluate the study bias. Continuous variables were expressed as mean±standard deviation(SD). A *p*-value <0.05 was considered statistically significant.

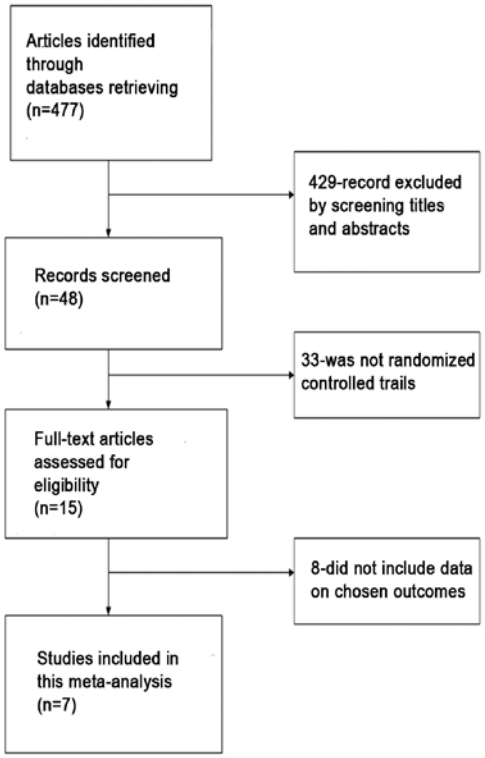

Figure 1 - Flowchart of the study selection process according to meta-analyses guidelines.

Results. *Search results.* The primary search retrieved 477 studies from PubMed, MEDLINE, the Cochrane Library, and EMBASE databases (**Figure 1**). After careful reviews, 48 studies were eligible for the inclusion criteria in this meta-analysis. The full manuscripts of the 48 studies were retrieved for detailed review. Following full manuscript review, an additional 39 studies were excluded: 33 studies were not randomized controlled trials; 8 studies did not report information on the chosen clinical outcomes.

Trial characteristics and study quality. We identified 7 randomized controlled trials on beta-blockers for inclusion in this meta-analysis, which enrolled a total of 1354 patients.[8-14] The mean follow-up duration was 16 weeks. Four trials reported on CCB therapy.[8,10,11,13] Two trials reported on ACEI therapy[12,14] and Stears et al used placebo as control.[9] According to the Cochrane Collaboration Handbook 5.0, 5 trials were qualified as high quality (A),[8,9,11-13] and 2 trails were qualified as Medium quality (B)[10,14] (**Table 1**).

Baseline patient characteristics. Baseline patient characteristics (**Table 2**) revealed remarkably similar ages in all trials. Most trials enrolled mostly men except for the trial by Phillips et al,[8] which enrolled 58.4% women. Most patients were overweight with the mean BMI ranging from 26-30 kg/m^2 except for patients in the studies by Phillips et al[8] and Bank et al[11] whose mean BMI was over 30 kg/m^2. The systolic blood pressure (SBP), remarkably similar in 5 studies, was restricted to 140 mm Hg; while SBP in the study by Östman et al[12] and Giugliano et al[13] was up to 160 mm Hg.

The effect of selective beta-1 blockers on glucose metabolism. The FBG data was extracted from all the 7 trails.[8-14] Six trails reported no statistically significant difference compared with the control group,[9-14] whereas

Table 1 - Randomized trials reporting the influence of selective beta-1 blockers on glucose metabolism.

Study	Year	Number of patients	Name of drug	Daily maintenance dose (mg)	Follow-up (week)	Study quality
Stears et al[9]	2012	Test: 41 Control: 37	Test: Atenolol Control: Placebo	50-100 50-100	4	A
Kveiborg et al[10]	2010	Test: 10 Control: 9	Test: Metoprolol Control: Carvedilol	200 50	8	B
Phillips et al[8]	2008	Test: 737 Control: 498	Test: Metoprolol Control: Carvedilol	400 50	20	A
Bank et al[11]	2007	Test: 18 Control: 16	Test: Metoprolol Control: Carvedilol	400 50	20	A
Ostman et al[12]	1998	Test: 34 Control: 26	Test: Metoprolol Control: Quinapril	100 20	24	A
Giugliano et al[13]	1997	Test: 22 Control: 23	Test: Atenolol Control: Carvedilol	50 25	24	A
Wang et al[14]	2005	Test: 47 Control: 45	Test: Bisoprolol Control: Captopril	5 25	12	B

A represent high quality, B represent medium quality

Table 2 - Patient characteristics in randomized trials of the effect of selective beta-1 blockers on glucose metabolism.

Study	Age (years)	Male (%)	SBP (mm Hg)	DBP (mm Hg)	Body mass index (kg/m²)	Primary outcomes
Stears et al[9]	62.5 (35-75)	59.0	143±14.25	86.2±10.05	29±4.65	FBG, 2hPBG, FINS, 30min PINS
Kveiborg et al[10]	58.5±2.8	72.4	142.9±5.1	71±3.5	28.6±1.5	FBG, FINS, HbA1c, BW, CRP
Phillips et al[8]	60.9±9.5	41.6	149.3±11.5	86.7±8.0	33.9±5.9	FBG, FINS, HbA1c, HOMA-IR, BW
Bank et al[11]	61.4±9.2	70.6	148±12	85±10	34±5.75	FBG, FINS, HbA1c, HOMA-IR, CRP
Östman et al[12]	64.5±7	61.7	167±15	98±5	28.6±3.3	FBG, HbA1c, FINS, BW
Giugliano et al[13]	57.8±6.3	55.5	162±13	98.5±4.2	28.1±3.9	FBG, HbA1c, FINS, BW
Wang et al[14]	60.8±9.2	54.3	147±8.0	88±8.4	26.3±3.3	FBG, HbA1c, 2hPBG

SBP - systolic blood pressure, DBP - diastolic blood pressure, BMI - body mass index, FBG - fasting blood glucose, 2hPBG- 2 hours postprandial blood glucose, HbA1c - glycosylated hemoglobin, FINS - fasting insulin, 30minPINS - 30 minutes postprandial insulin, HOMA-IR - insulin resistance index, BW - body weight, CRP - C-reactive protein.

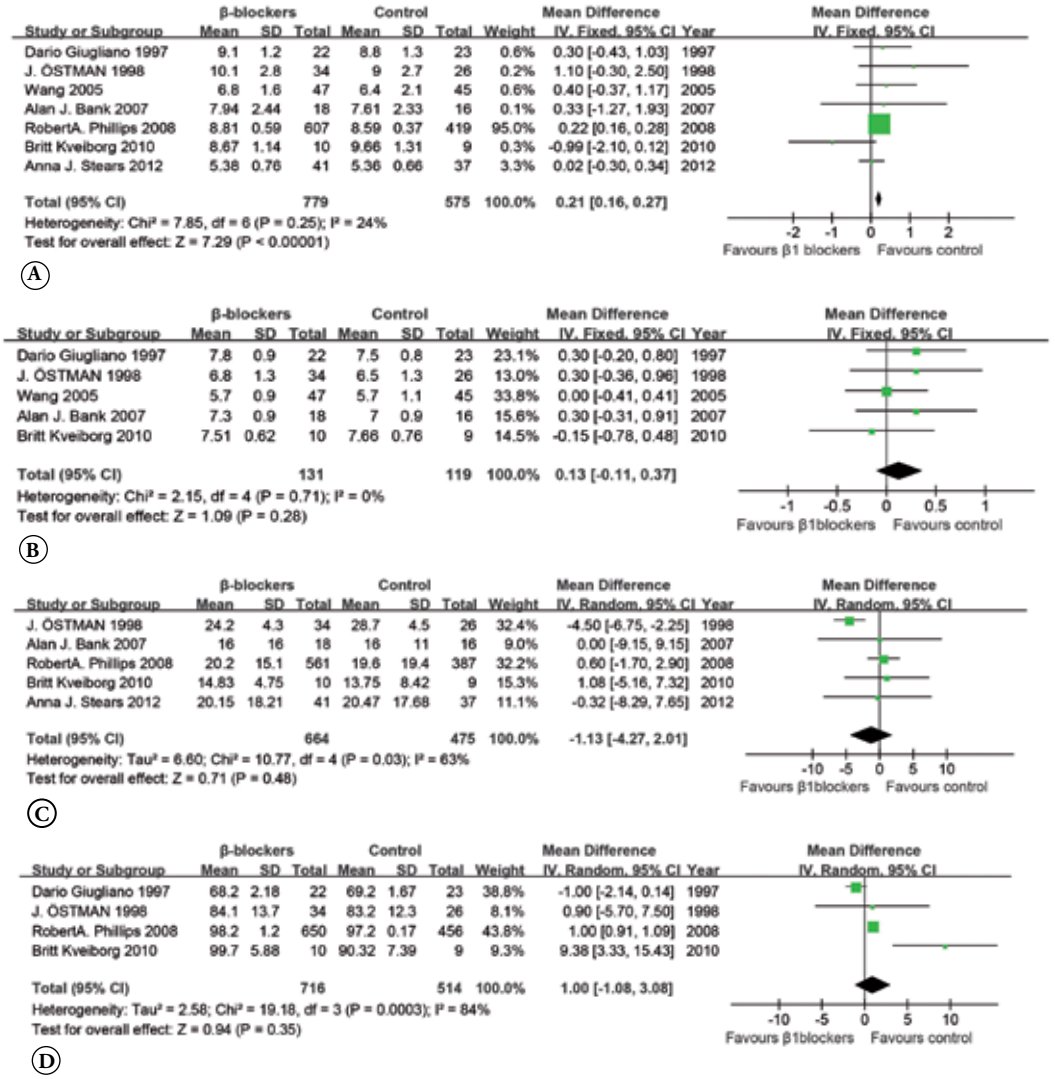

Figure 2 - Forrest plot and weight mean difference **A**) fasting blood glucose, **B**) glycosylated hemoglobin, **C**) fasting insulin, and **D**) body weight.

the study by Phillips et al[8] revealed the negative influence of selective beta-1 blockers on FBG. The meta-analysis indicated that selective beta-1 blockers were associated with a higher FBG (weight mean difference [WMD]: 0.21, 95% CI: 0.16 to 0.27; $p<0.001$) (**Figure 2A**)

Five trials reported the HbA1c data. All demonstrated no statistically significant difference when compared with the control group.[10-14] The meta-analysis showed that selective beta-1 blockers had no statistically significant effect on HbA1c (WMD: 0.13, 95% CI: -0.11-0.37; $p=0.28$) (**Figure 2B**).

The FINS data could be extracted from 5 trials.[8-12] Only Östman et al[12] reported a positive result on FINS that selective beta-1 blockers have less influence on FINS when compared with the control group. Other trials revealed no significant difference between the 2 groups.[8-11] The meta-analysis shows that the selective beta-1 blockers did not have a significant effect on FINS (WMD: -1.13, 95% CI: -4.27-2.01; $p=0.48$) (**Figure 2C**).

Four trials compared the effect on gain in body weight (BW).[8,10,12,13] Selective beta-1 blockers were associated with an increased weight gain in studies by Kveiborg et al,[10] and Phillips et al.[8] Whereas it revealed no significant difference by Östman et al[12] and Giugliano et al.[13] The meta-analysis declared no statistically significant difference (WMD: 1, 95% CI: -1.08-3.08; $p=0.35$) (**Figure 2D**).

Only the study by Stears et al[9] (WMD: 1.4, 95% CI: -2.88-5.68; $p>0.05$) and Phillips et al[8] (WMD: 0.4, 95% CI: -0.54-1.34; $p>0.05$) surveyed the effect of selective beta-1 blockers on HOMA-IR. Neither declared the effect as statistically significant.

Two studies investigated the influence of selective beta-1 blockers on CRP. Bank et al[11] observed no difference between groups (WMD: 0.10, 95% CI: -1.69-1.89; $p>0.05$), whereas Kveiborg et al reported[10] the change in CRP was in favor of the control group (WMD: 1.67, 95% CI: 0.61-2.73; $p<0.05$).

The I-square test of heterogeneity was relatively low in FBG with I^2 =24% and HbA1c with 0%. The I-square test of heterogeneity was high in FINS and BW with I^2 = 63% and 84%. The differences in therapies used as controls and duration of follow-up in each study caused the high heterogeneity which could not be eliminated. So, a random-effect modeling was conducted using the DerSimonian and Laird method in FINS, and BW.

Sensitivity analysis. The Phillips et al[8] trial reported the largest relative overall weight of 95% in FBG, 32.2%, in FINS, and 43.8% in BW. Therefore, we conducted a sensitivity analysis to assess the impact of this trial on the results. When excluding the Phillips' trial from the random effect estimates, there was no significant difference: WMD for FBG [0.09 (95% CI -0.17-0.34) $p=0.51$], WMD for FINS [-2.48 (95% CI -5.54-0.59) $p=0.11$], WMD for gain in BW [2.67 (95% CI -3.63-8.98) $p=0.41$]. The Ostman et al[12] and Wang et al[14] trials utilized ACEI as control therapy. When they were excluded from the analysis, no influence was exerted on the outcomes.

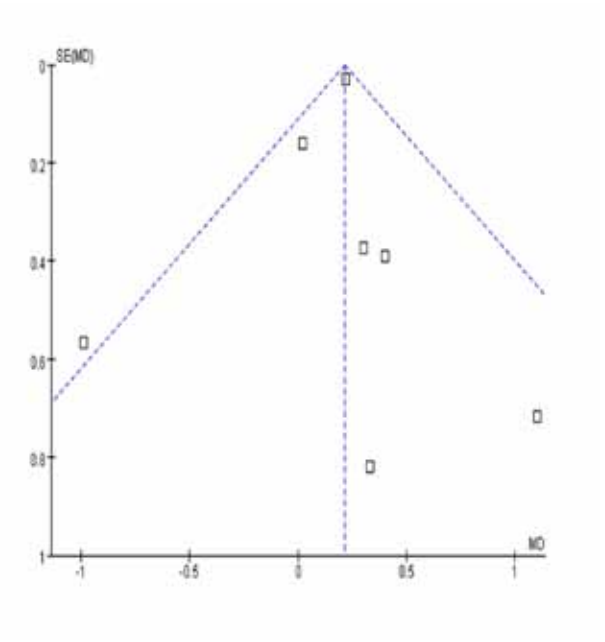

Figure 3 - Funnel plot of SE to evaluate publication bias for effect of beta-1 blockers in fasting blood glucose.

Publication bias. To assess a potential existence of publication bias in the effect of selective beta-1 blockers on FBG, a funnel plot as shown in **Figure 3** indicates slight asymmetry, and therefore a publication bias has likely existed.

Discussion. This is a meta-analysis combining results from 7 RCT's to investigate the effect of selective beta-1 blockers such as metoprolol, atenolol, and bisoprolol on T2DM patients with hypertension. We found that the selective beta-a blockers was inferior to ACEI and CCB on control of fasting blood glucose.

The prevalence of hypertension in patients who have T2DM is up to 3 times higher than in patients without diabetes. This can be partly explained by insulin resistance (IR) and chronic activation of the renin-angiotensin-aldosterone system (RAAS).[19] There is evidence that ACEI and ARB treatment increased first phase and second phase glucose stimulated insulin

secretion while conducting the blood pressure-lowering, RASS-inhibition, and cardio-protective effects.[20,21] Guidelines have already suggested that the primary antihypertensive drug strategy in patients with diabetes should include an ARB or an ACE inhibitor.[22] The CCB's are also associated with less diabetes,[23] and lower cardiovascular events.[24]

Beta-blockers are widely used in the clinical management of hypertension.[25] However, older beta -blockers are not preferred as first line agents, since some show adverse effects on glucose control and insulin sensitivity.[26] Evidence proves that highly selective beta-1 blockers produce greater improvements in cardiovascular protection,[27] and glucose tolerance.[7] On the other hand, Navare et al[28] enrolled 15 hypertensive adults and found that higher plasma atenolol exposure may be a risk factor for an increase in fasting plasma glucose levels. Yet Ayers et al[29] revealed that nebivolol lacked detrimental metabolic effects compared with early-generation beta-blockers (Metoprolol). Wang et al[14] enrolled 92 hypertensive patients with T2DM and found that bisoprolol appears to have a satisfactory hypotensive effect without any adverse effects on glucose metabolism. So, we undertook a meta-analysis of a wide range of highly selective beta-1 blockers including nebivolol, atenolol, and bisoprolol and only found that they were associated with elevated fasting blood glucose levels. Therefore, they should not be used for diabetic patients who require antihypertensive treatment, which indicates that further studies should not focus on highly selective beta-1 blockers to cure diabetic patients with hypertension. And other new drugs should be explored to treat these kinds of patients.

Study limitations. Some limitations in our meta-analysis should be considered. Firstly, the enrolled RCT's were mostly small randomized controlled trials and the deficiency of multi-center, large sample, high-quality trials made the study limited, which may affect the reliability of the results. Secondly, the methods of allocation concealment (randomization) were not clear in some trials; thus, increasing the chance of bias. Thirdly, inconsistencies existed in the control therapy, which included both ACE inhibitor and CCB. In fact, subgroup analyses should have been conducted, but due to the insufficient number of enrolled studies, all the studies underwent combined analysis.

In conclusion, our meta-analysis reveals that the highly selective beta-1 blockers were associated with elevated fasting blood glucose. Thus, highly selective beta-1 blockers are not suitable for patients with essential hypertension and diabetes which should provide theoretical guidance for the clinical treatment of T2DM patients with hypertension.

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