Systematic Review and Meta-Analysis

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A systematic review and meta-analysis of the impact of mineralocorticoid receptor antagonists on glucose homeostasis

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Abstract

Background: Spironolactone, a nonselective mineralocorticoid receptor antagonist (MRA), may have a deleterious effect on glycemia. The objective of this review was to assess current knowledge on MRAs' influence (spironolactone, eplerenone, and canrenone) on glucose homeostasis and the risk of diabetes.

Method: A systematic review was conducted using the Medline database on articles published from 1946 to January 2017 that studied the effects of MRAs on any glucose-related endpoints, without any restrictions regarding the participants' characteristics.

Study design, patient population, dose and duration of intervention, and the quantitative results on glycemic markers were extracted, interpreted for result synthesis, and evaluated for sources of bias. From the articles included in the qualitative analysis, a select number were used in a meta-analysis on studies having measured glycated hemoglobin (HbA_{1c}) or risk of diabetes.

Results: Seventy-two articles were selected from the Medline database and references of articles. Results on spironolactone were heterogeneous, but seemed to be disease-specific. A potential negative effect on glucose regulation was mainly observed in heart failure and diabetes trials, while a neutral or positive effect was detected in diseases characterized by hyperandrogenism, and inconclusive for hypertension. Interpretation of data from heart failure trials was limited by the small number of studies. From a meta-analysis of 12 randomized controlled studies evaluating spironolactone's impact on HbA_{1c} in diabetic patients, spironolactone had a nonsignificant effect in parallel-group studies (mean difference 0.03 [−0.20;0.26]), but significantly increased HbA_{1c} in crossover studies (mean difference 0.24 [0.18;0.31]). Finally, eplerenone did not seem to influence glycemia, while limited data indicated that canrenone may exert a neutral or beneficial effect.

The studies had important limitations regarding study design, sample size, duration of follow-up, and choice of glycemic markers.

Conclusion: Spironolactone may induce disease-specific and modest alterations on glycemia. It is uncertain whether these effects are transient or not. Data from the most extensively studied population, individuals with diabetes, do not support a long-term glycemic impact in these patients. Further prospective studies are necessary to establish spironolactone's true biological effects and their clinical implications.

Abbreviations: 11β-HSDII = 11β-hydroxysteroid dehydrogenase type II, ACTH = adrenocorticotropic hormone, AGT = abnormal glucose tolerance, AUC = area under the curve, BMI = body mass index, CV = cardiovascular, EPLE = eplerenone, HbA_{1c} = glycated hemoglobin, HCTZ = hydrochlorothiazide, HF = heart failure, HOMA-βF = homeostatic model assessment of β-cell function, HOMA-IR = homeostasis model assessment of insulin resistance, IRI = immunoreactive insulin, MRA = mineralocorticoid receptor antagonist, NGT = normal glucose tolerance, OC = oral contraceptive, OGTT = oral glucose tolerance test, PCOS = polycystic ovary syndrome, QUICKI = quantitative insulin sensitivity check index, RAAS = renin-angiotensin-aldosterone system, RCT = randomized controlled trial, SPIRO = spironolactone, TCTZ = trichlormethiazide.

Keywords: glucose, glucose metabolism disorders, glycosylated hemoglobin A, meta-analysis, mineralocorticoid receptor antagonists, review, spironolactone

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1. Introduction

Increased activity of the renin-angiotensin-aldosterone system (RAAS) is present in many cardiovascular (CV) diseases, including hypertension and heart failure (HF).[1] Aldosterone contributes to many of the negative processes related to RAAS in these pathologies, such as myocardial fibrosis, sodium retention, increased blood pressure, and inflammation.[1] Mineralocorticoid receptor antagonists (MRAs), such as spironolactone (SPIRO) and eplerenone (EPLE), block the deleterious effects of aldosterone that are mediated by the mineralocorticoid receptor. Consequently, this pharmacological activity makes MRAs effective in treating hypertension, particularly resistant hypertension,[2] and in reducing the risk of morbidity and mortality in HF patients.[3–6] MRAs are also used for the treatment of primary aldosteronism[7] and edema associated with liver cirrhosis or nephrotic syndrome.[8]

Despite its beneficial impact on CV events, SPIRO, a nonselective MRA, has "off-target" effects on progesterone, androgen, and glucocorticoid receptors. These effects include the displacement of androgen from the androgen receptor, inhibition of enzymes in the testosterone synthesis pathway (17α-hydroxylase and 17–20 desmolase), increases in the conversion of testosterone to estradiol,[9,10] and inhibition of estrone sulfatase and 17β-HSD type 1 which leads to increases in estradiol pool.[11] These mechanisms cause gynecomastia, breast tenderness, menstrual irregularities,[9] and erectile dysfunction.[12] Although these off-target effects are undesirable in most conditions, they are useful for the treatment of disorders related to hyperandrogenism.[13,14] Thus, SPIRO is also a treatment for idiopathic hirsutism[13] and polycystic ovary syndrome (PCOS), a disease characterized by excess androgens, oligoovulation or anovulation and/or polycystic ovaries.[14]

There is a growing amount of evidence suggesting that SPIRO's "off-target effects" could also include detrimental effects on glucose homeostasis.[15–86] A potential cause of this negative effect is the fact that SPIRO increases cortisol levels through an off-target effect: the blockade of the glucocorticoid receptors.[64] Cortisol, a glucocorticoid, increases glucose through lipolysis and gluconeogenesis. On the other hand, EPLE, a selective MRA, has a very low activity on other steroid receptors.[87] As such, it is believed that it does not inhibit adrenal cell aldosterone or cortisol production and does not affect glucose metabolism.

Glucose intolerance and diabetes are already frequent comorbidities in some of the diseases that require treatment with an MRA, and are associated with an increased risk of CV events.[88–90] Thus, it is critical to determine if MRAs modulate glycemia in any of the patient populations that use them. The objective of this article was to assess current knowledge on the subject in existing literature, in the context of growing use of MRAs in HF and in other diseases. Also, the information on potentially additional adverse effects of MRAs could be used by physicians to guide their treatment choices. We conducted a systematic review of randomized controlled trials (RCTs), prospective studies, and observational studies, evaluating the influence of the MRAs SPIRO, EPLE, and canrenone, regardless of comparator group, on any biomarkers of glucose homeostasis in a variety of populations. Healthy individuals, patients at risk of CV disease, HF patients, and patients with other non-CV diseases were included into this analysis. We then performed a meta-analysis with appropriate datasets.

2. Methods

2.1. Search strategy

A search was conducted on the Medline database on articles written from 1946 till January 2017. In addition, a manual search was performed on references of the retrieved articles from Medline, based on the eligibility criteria. The following search terms were used: glucose, or glucose metabolism disorders, or insulin, or glycosylated hemoglobin A; and steroid receptors, or aldosterone, or mineralocorticoid receptor antagonists, or spironolactone, or eplerenone; and humans, or double-blind method.

2.2. Eligibility criteria

Any prospective RCTs or prospective or retrospective cohort studies that contained measures of glucose metabolism, before and after treatment with an MRA, were reviewed. We did not put any constraints on the types of glycemic markers, because we wished to collect any information that was relevant to the effect on glucose control. MRAs were restricted to SPIRO, EPLE, and canrenone (an active metabolite of SPIRO). The MRA drospirenone was excluded because it is mainly used as a contraceptive. There were no limitations for the comparator or the absence of a comparator. However, studies in which an MRA was evaluated in combination with another drug but without any comparator group were excluded. For example, in the case where a combination of SPIRO with a thiazide diuretic was being used, the article was accepted only if the study design included a comparator group consisting of either 1 of these 2 drugs in monotherapy. A minimum treatment period with an MRA of 1 week was required for inclusion. As we were interested in comparing the effects of MRAs in various diseases, we included studies irrespective of study population (healthy, at risk of CV disease, HF, and other non-CV diseases), or whether the effect on glucose metabolism was part of the primary or secondary endpoints. We limited our language selection to English, French, and Russian.

2.3. Study selection, data extraction, and synthesis of results

Eligibility assessment and data collection was performed independently by the first and second authors. Any differences were resolved through discussions and consensus. Articles were selected after an evaluation of the title, abstract, or full article. The results on Medline were alphabetized by the first author's name in each study, to easily identify and eliminate duplicates. Data extraction was conducted using an MsExcel spreadsheet. The following characteristics were extracted: study design, sample size, disease of participants, study medication and dose, time of treatment and follow-up, the markers of glucose homeostasis, and effects of the study medication on the markers.

Although all markers of glucose homeostasis were collected for the systematic review, our primary endpoints were the change in glycated hemoglobin (HbA_{1c}) and onset of diabetes in the context of RCTs, as these are markers of long-term glucose control. All available summary measures of glycemic markers were recorded: baseline and posttreatment means or medians, mean changes within treatment groups or treatment phases, mean differences between groups, and odds ratios or risk ratios.

2.4. Meta-analysis

Prospective RCTs that evaluated SPIRO's effect on HbA_{1c} and that had a comparator group were also included into quantitative

analyses. As HbA_{1c} is an indicator of glucose control over a period of 3 months, we considered it to be the most reliable marker to include in the meta-analysis, as opposed to glucose or insulin that may vary greatly between blood tests. HbA_{1c} data is reported as a mean difference (MD) and accompanying 95% confidence interval (CI) and was pooled using a Hartung-Knapp method random-effects model with the "meta" package in R version 3.1.3 (The R Project for Statistical Computing).[91] Separate analyses were conducted for parallel-group versus crossover studies. We assessed presence of statistical heterogeneity using the Cochrane P value ($P < .10$ significant) and the degree of heterogeneity using the I^2 statistic with a value >50% considered substantial.[92]

2.5. Quality and risk of bias

The first and second authors evaluated independently the quality and the risk of bias of each study considering the following criteria: study design (retrospective vs prospective; observational vs interventional), randomization, blinding (double-blind vs single-blind vs open-label), trial registration, choice of comparator, presence of a washout period, dose of study medication and regimen, duration of treatment and follow-up, sample size and statistical power, choice of glycemic markers, analytical methods, baseline characteristics/medication and between-group imbalances, quality of laboratory measurements, line of therapy for an MRA, and comprehensive description of methodology and results. However, we did not exclude studies based on this evaluation.

2.6. Ethical review

Ethical approval was not necessary for this study as it only included previously published summary data. It did not involve animal or human test subjects, and did not require access to any personal data.

3. Results

Figure 1 presents the selection process. From 1682 articles that were identified through the Medline database (excluding duplicates), 117 articles were excluded due to language barriers and 338 reviews were removed. Among the remaining articles, 873 were excluded from the title and 259 were excluded for the abstract. Finally, 35 articles were removed after reading the full text. An additional 12 articles were identified from the references of the articles that were found in the Medline search results. Thus, 72 articles were included into this literature review. Among these articles, 12 studies were chosen to be included in the meta-analysis according to our selection criteria, as they consisted of RCTs measuring effects on HbA_{1c}. We did not have a sufficient number of studies on the risk of diabetes.

Tables 1–8 present each study's characteristics. Studies were grouped according to different patient populations. A variety of markers of glycemia were evaluated. Synthesis of the findings

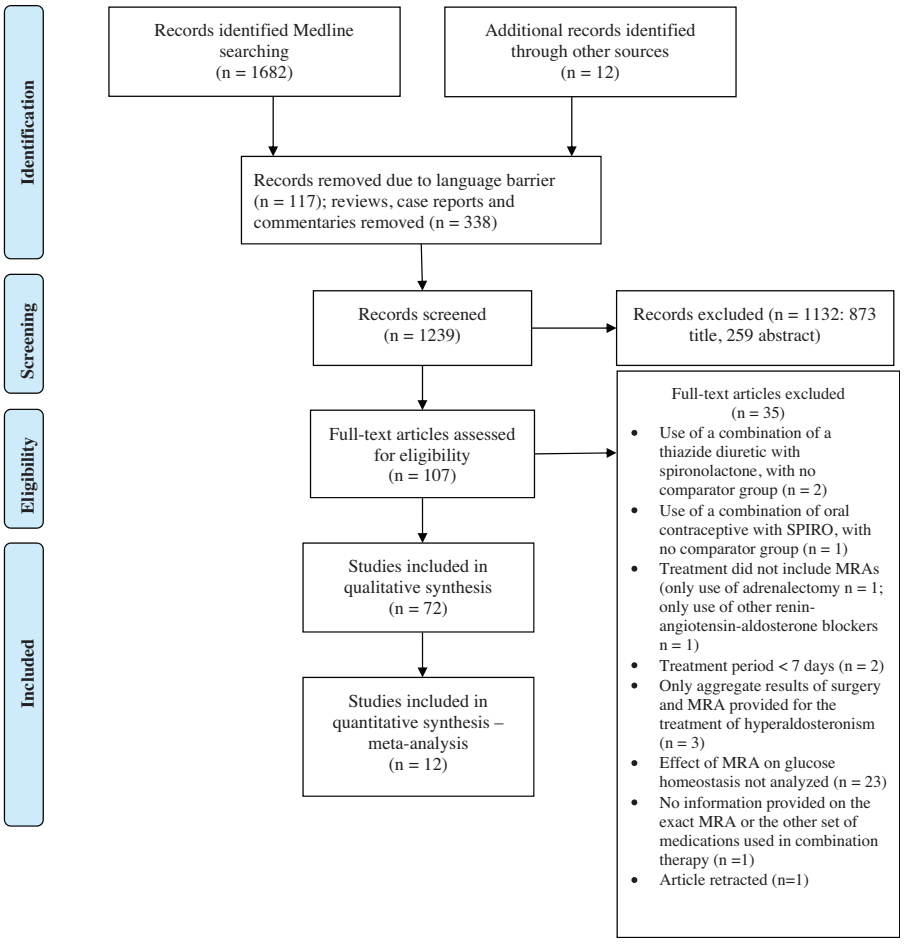

Figure 1. Flow of information.

Table 1

Results for healthy volunteers.

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Clore JN[15]	1988	Prospective, no randomization reported	18 men on normal diet	10 d	First period: 5 d electrolyte stabilization followed by 5 d of steroid administration (ACTH or cortisol) Second study period, days 1 to 10: SPIRO 100 mg every 6 h (with ACTH or cortisol) Other: RU486 (glucocorticoid receptor antagonist) every 6 h with cortisol or alone	SPIRO did not affect progressive increase in cortisol and 17OHCS excretion during ACTH or cortisol administration, SPIRO did not affect the increase in glucose caused by administration of cortisol RU486: significantly lower glucose concentration, failure of insulin to increase during cortisol administration compared with control value
Krug AW[16]	2013	Prospective, no control group	13 healthy adult males	14 d	EPLE 50 mg/d	No change in HOMA-IR, insulin, or glucose

17OHCS = 17 hydroxycorticosteroid, ACTH = adrenocorticotropic hormone, EPLE = eplerenone, HOMA-IR = homeostasis model assessment of insulin resistance, SPIRO = spironolactone.

according to each disease is presented in Table 9, grouped according to healthy individuals, patients at risk of CV complications, HF patients, and patients suffering from other illnesses unrelated to CV disease. Limits of each individual study can be accessed in the Supplemental Content, http://links.lww.com/MD/B966.

3.1. Qualitative review

3.1.1. Healthy volunteers. Only 2 small prospective studies were conducted on 18 and 13 healthy volunteers, and had a short follow-up period of 10 and 14 days, respectively (Table 1).[15,16] The first study compared the use of high dose SPIRO (100 mg every 6 hours) in combination with adrenocorticotropic hormone (ACTH) or cortisol versus a glucocorticoid receptor antagonist (RU486).[15] The second study included the use of 50 mg EPLE, without a comparator group.[16] In both studies, the MRA exerted a neutral effect on glucose control, although HbA_{1c} or the risk of diabetes was not evaluated.

3.1.2. Hypertension. We identified multiple studies (14 studies) that were performed on hypertensive patients. Eleven studies used SPIRO, and 3 used EPLE (Table 2). Studies with SPIRO included 7 RCTs,[17–23] 1 prospective nonrandomized trial without controls,[24] and 3 observational studies.[25–27] Studies with EPLE consisted of 1 RCT[28] and 2 prospective trials without control groups.[29,30]

Sample sizes varied from 15 to 1141 patients, and study duration varied between 2 months and 10 years. Doses ranged from 25 to 100 mg/d for SPIRO,[18–22,24–27] with the exception of 2 studies, where doses went up to 200[17] and 400 mg.[23] EPLE was used at doses of 25 to 50 mg.[28–30] Although a number of biomarkers were used to evaluate the effect of the MRAs on glycemia, only 3 studies measured the effect on HbA_{1c}.[22,24,30] The onset of diabetes was not assessed in any of the studies. The markers that were measured included: glucose, insulin, area under the curve (AUC) glucose, AUC insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI).

Results for SPIRO were heterogeneous. In studies that compared SPIRO to placebo or that lacked a comparator group, SPIRO exerted a negative or slightly negative effect on some glycemic markers.[24,26,27] In most studies comparing SPIRO to chlorthalidone, SPIRO had a more beneficial effect on glycemia than its comparator.[19,21] Use of SPIRO in comparison to or in combination with hydrochlorothiazide, or in comparison to trichlormethiazide, did not yield any conclusive results.[22,23,25] It is worth mentioning that thiazide diuretics are known to be associated with worsening glucose control.[52] One study comparing SPIRO to perindopril or placebo did not find any significant differences between groups in terms of glucose.[18] On the other hand, EPLE exerted a neutral effect in all reports.[28–30]

3.1.3. Obesity and metabolic syndrome. Two RCTs evaluating the effect of SPIRO were conducted on obese individuals (Table 3).[31,32] Seven studies were done on patients with metabolic syndrome. Among these studies, 3 evaluated the effect of SPIRO.[33–35] They consisted of 1 RCT[33], 1 prospective nonrandomized trial,[34] and 1 prospective trial without a control group.[35] One randomized, double-blind, placebo-controlled, parallel-group study compared directly SPIRO to EPLE, as well as to a placebo group.[36] Another RCT (crossover) compared EPLE to placebo.[37] The last 2 studies were double-blind placebo-controlled trials on canrenone; however, the allocation was based on blood pressure characteristics rather than randomization (Table 3).[38,39]

The sample sizes ranged from 8 to 156 patients, with study duration lasting from 1 month (treatment period in crossover study) to 9 months. SPIRO was used at doses of 25 to 75 mg, EPLE doses ranged from 25 to 100 mg, and doses of canrenone were between 50 and 100 mg. A variety of biomarkers were also measured in these study populations, such as glucose, insulin, HOMA-IR, AUC glucose, AUC insulin, insulin sensitivity index, glucose effectiveness, and IV glucose tolerance. HbA_{1c} and onset of diabetes were not measured in any of these studies.

These few small studies suggest that SPIRO does not exert a negative effect on glucose control in patients with obesity or metabolic syndrome, although their statistical power was limited. EPLE, a selective MRA, was not found to have a significant effect on glycemia. Studies with canrenone, which is more selective for the mineralocorticoid receptor than SPIRO,[93] suggest that it may exert a beneficial effect in this population.

3.1.4. Diabetes. Multiple studies were conducted on patients with diabetes. Indeed, we identified 20 prospective studies that were performed on diabetic patients (Table 4).[40–59] SPIRO was used in 16 of these studies, with 15 RCTs[40–54] and 1 prospective study without controls.[55] Three RCTs used EPLE,[56–58] and 1 RCT was performed with canrenone.[59]

Sample sizes varied greatly between 16 and 268 patients. Study duration was between 8 weeks and 1 year, with the exception of 1 study that had a treatment period of 1 week. SPIRO was given

Table 2

Results for hypertension.

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Scherstén B[17]	1980	Prospective, double-blind, multicenter (crossover)	45 patients with primary hypertension	11 mo	SPIRO 50, 100, 200 mg and placebo: 3 treatment periods of 2 mo, intervening placebo periods 1 to 2 mo	No change in glucose levels
Plouin PF[18]	1991	Randomized, double-blind, placebo-controlled, parallel-group trial	75 hypertensive patients aged 50 y and older, with 25 per group (9 patients withdrawn during trial, 5 from SPIRO group)	8 wk (after 2-wk run-in period)	SPIRO 37.5 to 75 mg/d (high dose if diastolic blood pressure>90 mm Hg) versus perindopril 4 to 8 mg/d versus placebo	Effect on fasting blood glucose not significantly different between groups (week 0 to week 8: placebo 5.1 ± 0.1 to 5.0 ± 0.1 mmol/L; perindopril 5.0 ± 0.1 to 4.9 ± 0.1 mmol/L; SPIRO 4.9 ± 0.1 to 4.8 ± 0.1 mmol/L; treatment-time interaction $P > .9$)
Raheja P[19]	2012	Randomized, single-blind, crossover design	17 patients with hypertension	12 wk	Chlorthalidone or chlorthalidone with SPIRO 25 mg/d or chlorthalidone with irbesartan	SPIRO attenuated insulin resistance caused by chlorthalidone: SPIRO returned HOMA-IR and serum insulin levels to baseline values Difference chlorthalidone versus chlorthalidone with SPIRO: Glucose $P < .05$ HOMA-IR $P < .01$
Menon DV[20]	2009	Randomized, single-blind, crossover study	23 patients with hypertension	3 mo	SPIRO 50 to 75 mg/d or chlorthalidone	Increase in plasma glucose from 92.2 ± 2.0 to 99.6 ± 2.7 ($P < .01$ versus baseline) with SPIRO versus similar increase in comparator chlorthalidone 101.6 ± 3.3 ($P < .01$ versus baseline) (ANOVA $P = .001$ difference between baseline and 2 treatment phases) No effect on insulin, QUICKI or HOMA-IR, contrary to chlorthalidone
Ames RP[21]	1984	Randomized, unblinded study Patients recruited from MRFIT trial (randomized primary prevention trial)	23 patients with hypertension (11 on SPIRO): men on diuretics with increased cholesterol	2 to 4 mo	SPIRO (11 patients) versus chlorthalidone (10 patients) or HCTZ (2 patients) Same dose as chlorthalidone	Fasting glucose levels lower during period of treatment with SPIRO than with chlorthalidone ($P < .05$), but no significant change observed within SPIRO group
Yutaka M[22]	2009	Prospective, randomized trial	64 patients with hypertension	6 mo	SPIRO 25 mg versus HCTZ 2 mg 3 d/wk (added to baseline antihypertensive therapy ACE inhibitor/ARB)	No significant change in either group in fasting plasma glucose or fasting plasma insulin Borderline significant decrease in HbA_{1c} with SPIRO (5.4 ± 0.4 to 5.3 ± 0.4%, $P = .0471$)
Schrijver G[23]	1979	Prospective, double-blind, randomized study	49 patients with mild to moderate essential hypertension	12 wk	HCTZ 100 mg/d or SPIRO 100 mg/d or SPIRO 200 mg/d or SPIRO 400 mg/d; After 8 wk: each group divided into 1 subgroup with addition of 100 mg/d HCTZ and another subgroup with addition of placebo	Single-drug treatment phase: significant rise in blood glucose only with SPIRO 400 mg/d ($P < .05$) Double-drug treatment phase: significant decrease in glucose levels with SPIRO 100 mg/d plus placebo ($P < .05$) and significant increase in glucose levels

(*continued*)

Table 2
(continued).

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
						with SPIRO 400 mg/d plus placebo ($P < .05$)
Falch DK[24]	1983	Prospective, no randomization, no control group	15 males with primary hypertension	1 y	SPIRO 100 mg/d (measure at baseline, 6 and 12 mo)	Glucose unchanged, transient increase in insulin of 78.8% after 6 mo, AUC unchanged for glucose, and transient increase at 6 mo of insulin response curve by 55.2%, H indices unchanged: transient glucose intolerance HbA_{1c} unchanged from 6 to 12 mo (not measured at baseline)
Jeunemaitre X[25]	1988	Observational cohort study, patients referred to the St. Joseph and Broussais hypertension clinics in Paris between January 1, 1976 and January 1, 1986	300 patients in study (100 on SPIRO) with essential hypertension	From 1976 to 1986 (mean 20 mo)	SPIRO or HCTZ with amiloride or cyclothiazide with triamterene, mean dose 98 mg	No change in fasting blood glucose with SPIRO, slight increase with HCTZ-amiloride (phenomenon of regression to the mean)
Jeunemaitre X[26]	1987	Observational prospective cohort study: information prospectively collected from data bank from 1976 to 1985 (20,812)	182 patients with essential hypertension	691 d (23 mo, almost 2 y)	SPIRO monotherapy, mean dose 96.5 mg	No significant change in glucose levels (slight increase in men)
Chapman N[27]	2007	Substudy of a large-scale, multicenter, randomized, open-label, controlled trial: observational, not placebo-controlled	1141 patients with essential hypertension, prescribed SPIRO as a fourth line antihypertensive agent	1.3 y (median duration treatment)	SPIRO, median dose 25 mg, randomly assigned to either amlodipine or atenolol	Modest but significant increase in fasting plasma glucose: 7.11 (2.62) to 7.30 (2.75)-mean difference 0.19 ($P = .005$)
McMurray EM[28]	2014	Randomized, controlled, double-blind, crossover trial	15 patients with essential hypertension	12 wk each treatment (6 wk washout from antihypertensive medication, 12 wk treatment, 6 wk washout, 12 wk crossover medication)	EPLE 25 mg twice/d versus doxazosin 2 mg twice/d	No significant differences in fasting glucose and fasting insulin between treatments Glucose clamp studies: Insulin sensitivity similar in both treatments ($P = .83$) Small difference in insulin concentration in last 30 min of insulin infusion No significant difference in endogenous glucose production or peripheral glucose utilization rates (nonsignificant lower endogenous glucose production following treatment with eplerenone 2.0 (0.8) μmol/kg × min versus 4.1 (0.9) μmol/kg × min after doxazosin ($P = .085$)
Yano Y[29]	2011	Prospective, no control group	20 elderly patients with essential hypertension	24 wk		No significant change in fasting glucose ($P = .846$) and insulin ($P = .466$)

(*continued*)

Table 2
(continued).

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
					EPLE 25 mg/d (10 patients), 50 mg/d (10 patients): mean 37.5 ± 12.8 mg/d (added to ACE inhibitor/ARB)	
Sato A[30]	2010	Prospective, open-label, no control group	68 patients with essential hypertension	24 wk	EPLE 50 mg (in addition to an ACE inhibitor imidapril or long-acting CCB amlodipine)	No change in HbA_{1c}

AUC = area under curve, EPLE = eplerenone, HbA_{1c} = glycated hemoglobin, HCTZ = hydrochlorothiazide, HOMA-IR = homeostasis model assessment of insulin resistance, QUICKI = quantitative insulin sensitivity check index, SPIRO = spironolactone, TCTZ = trichlormethiazide.

at doses of 25 to 50 mg. EPLE doses ranged between 50 and 100 mg, and canrenone was given at a dose of 25 mg. Measured biomarkers included cortisol, glucose, insulin, HOMA-IR, HOMA-β, adiponectin, and fructosamine. In contrast with other diseases, almost all of the studies (18 studies) assessed the effect on HbA_{1c}. This parameter increased between 0.16% and 0.6% with the use of SPIRO in studies that detected a significant association between SPIRO and changes in HbA_{1c}.

Sixteen studies evaluated SPIRO. Among the 15 studies that measured HbA_{1c}, 6 studies found that it significantly impaired glucose control,[40–43,48,49] and 3 observed a nonsignificant, harmful trend with this drug.[44,45,51] We must mention that 2 of these studies, conducted by the same group, had similar and overlapping populations.[48,49] Thus, the second study[49] was not included in the meta-analysis. Three studies that did not find a significant change in glucose metabolism with SPIRO used a placebo[46,47] or no comparator.[55] Another study that reported no significant change compared SPIRO with losartan,[50] a drug from a pharmacological class that is known to decrease the risk of diabetes.[94] The other 2 studies that did not find a significant change used hydrochlorothiazide as a comparator,[51,52] which, as previously mentioned, is known to cause hyperglycemia.[52] In the 3 EPLE studies, there was no significant impact on glycemia. Moreover, adiponectin, a protective adipocytokine, increased with EPLE in one of the studies.[58] Similarly, canrenone did not influence glucose metabolism in this population.

3.1.5. Heart failure. We found a limited number of studies in HF. Among a total of 5 studies that were conducted on HF patients,[60–64] 2 studies used SPIRO and consisted of 1 RCT[60] and 1 retrospective cohort study.[61] Two substudies of large RCTs used EPLE.[62,63] Finally, 1 RCT compared directly the 2 drugs (Table 5).[64]

Sample sizes in this disease were quite large, ranging between 107 and 6497 patients, with the exception of 1 study that included 16 patients. The duration of the studies varied from 4 months to 2.8 years. SPIRO was used at doses of 25 mg, while EPLE was administered at doses of 25 to 50 mg. Many biomarkers were measured, including glucose, insulin, HOMA-IR, cortisol, and adiponectin. Most notably, HbA_{1c} (in 1 study[64]) and the incidence of diabetes[61,62] were measured for this disease.

SPIRO had a deleterious effect on glucose homeostasis in HF patients. HbA_{1c} increased by 0.2%.[64] Furthermore, this negative effect correlated with an increase in cortisol levels,[64] suggesting that SPIRO exerts its negative effect through an increase in this hormone. On the other hand, EPLE did not have any effect on glucose homeostasis.

3.1.6. Polycystic ovary syndrome and idiopathic hirsutism. Fourteen studies evaluated the effect of SPIRO on patients with disorders related to hyperandrogenism (polycystic ovary syndrome [PCOS] or idiopathic hirsutism) (Table 6).[65–78] Among this large number of studies, 7 were RCTs,[65–71] 4 studies were prospective but without controls,[72–75] 2 studies were prospective with medication assigned based on each patient's needs,[76,77] and one study was of observational design.[78]

Sample sizes and duration of follow-up were somewhat limited. Almost all of the studies had sample sizes from 14 to 100 patients. Only 1 study included >100 patients (total sample of 198 patients).[65] Study duration was between 2 weeks and 12 months. The doses of SPIRO ranged from 50 to 200 mg, and were usually higher than those used in other diseases. Although a number of biomarkers were collected, none of the studies measured levels of HbA_{1c} or the incidence of diabetes. Rather, the

Table 3

Results for obesity or metabolic syndrome.

Author	Year	Study design	Patients Disease	Follow-up	Medication Dose	Results of markers
Garg R[31]	2014	Placebo-controlled, double-blind, randomized, parallel group study	32 obese individuals (BMI >30 kg/m^2)	6 wk	SPIRO 50 mg/d versus placebo	No significant effect on HOMA, area under the curve for insulin or glucose, insulin sensitivity index in either groups
Lovejoy JC[32]	1996	Randomized, double-blind, placebo-controlled, parallel-group trial, 3 groups matched by a blocking strategy for age, waist to hip ratio, and blood pressure	30 healthy obese postmenopausal women, 10 in each group (3 dropped-out, 1 from SPIRO group)	9 mo	SPIRO 75 mg/d versus nandrolone decanoate 30 mg/2 wk (weak androgen) versus placebo, added to low-fat weight reducing diet	No significant treatment effects on fasting glucose, insulin, insulin sensitivity index (S_I), glucose effectiveness (S_G), iv glucose tolerance (K_G)
Kosmala W[33]	2011	Prospective, double-blinded, parallel-group, placebo-controlled trial	80 patients (40 patients on SPIRO) with metabolic syndrome (already treated with angiotensin II inhibition)	6 mo	SPIRO 25 mg/d versus placebo	No significant changes in fasting insulin, fasting glucose or HOMA-IR
Costa MB[34]	2010	Prospective, double-blind, no randomization, no crossover: SPIRO followed by placebo in all patients	11 patients with metabolic syndrome and hypertension	Washout period of 2 wk, 8 wk of treatment with SPIRO, 8 wk of treatment with placebo	SPIRO 25 to 50 mg/d versus placebo	No significant changes in glucose metabolism (but in table significant decrease in glucose in SPIRO phase, and slight decrease in HOMA IR) Glucose: basal 99±9.2 mg/dL, SPIRO 86±14.2 mg/dL ($P<.05$), placebo 86±12.7 mg/dL; HOMA-IR: basal 3.3 ±2.49, SPIRO 2.7±1.95 (P not indicated so probably $P>.05$), placebo 2.4±1.66 Comparator: Decrease, but no change between SPIRO and placebo
Lovisi JCM[35]	2011	Prospective, no control group	19 patients with metabolic syndrome	16 wk	SPIRO 50 mg/d	Nonsignificant improvement in HOMA-IR 4.52±6.85 to 3.6 ±2.25 ($P=.580$) Small nonsignificant increase in glucose (not mentioned in article): 92.1 ±8.19 to 93.4±9.31 ($P=.460$)
Kanchan V[36]	2016	Randomized, double-blind, placebo-controlled, parallel group study	60 patients (20 per group) with metabolic syndrome	12 wk	SPIRO 25 mg/d versus EPLE 25 mg/d versus placebo	No significant effect on fasting plasma glucose, fasting plasma insulin, or HOMA-IR
Hwang MH[37]	2015	Balanced (by sex), randomized, double-blind, placebo-controlled, crossover study	8 patients with metabolic syndrome	3 mo (1 mo treatment period separated by 1 mo washout period)	EPLE 100 mg/d versus placebo	No change in insulin resistance (HOMA-IR 1.04±0.26 vs 1.38±0.50, $P=.6$) Alternate hypothesis was that it would exert a beneficial effect (no precision whether t test was 1 sided)
Derosa G[38]	2013	Double-blind, placebo-controlled study	145 patients (141 completed) with metabolic syndrome	6 mo	Canrenone 50 mg/d for 3 mo, then 50 mg twice a day till 6 mo (patients with metabolic syndrome and blood pressure >130/85 mm Hg) versus placebo (patients without the blood pressure characteristic)	Significant decrease in fasting plasma glucose (118.3±7.2 to 95.8±4.6 mg/dL, $P<.05$) compared to baseline Significant decrease in fasting plasma insulin (16.8±4.9 to 10.1 ±3.2 μU/mL) and HOMA-IR (4.91±1.07 to 2.39± 0.58) compared with baseline ($P<.05$) and placebo ($P<.05$) Significant increase in M value (insulin sensitivity—2.82± 0.71 to 3.29±0.96 μmol/min/kg) compared with baseline ($P<.05$) and placebo ($P<.05$)
Derosa G[39]	2015	Double-blind, placebo-controlled study	156 patients (153 completed the study) with metabolic syndrome	6 mo	Canrenone 50 mg/d for 3 mo, then 50 mg twice/d until end of study (patients with metabolic syndrome and blood pressure >130/85 mm Hg) versus placebo (patients without the blood pressure characteristic)	Fasting plasma glucose: significantly decreased with canrenone (117±7.4 to 98.2±5.0 mg/dL), $P<.05$ versus baseline, $P<.05$ versus placebo No decrease in placebo

BMI = body mass index, HOMA-IR = homeostasis model assessment of insulin resistance, M-value = insulin sensitivity, SPIRO = spironolactone.

Table 4

Results for diabetes.

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Swaminathan K[40]	2008	Randomized, placebo-controlled, double-blind, crossover study	50 patients with diabetes and hypertension (38 completed the study)	10 wk (4 wk treatment periods separated by 2 wk washout)	SPIRO 25 to 50 mg/d or placebo for 4 wk, then 2 wk of washout, then 4 wk crossover	Significant increase with SPIRO: 0.21% in HbA_{1c} compared to placebo ($P=.01$), mean difference in cortisol of 92.4 nmol/L compared to placebo ($P=.003$) Worse effect with SPIRO
Davies JI[41]	2004	Prospective, randomized, double-blind trial (crossover)	42 patients with diabetes, without HF (baseline characteristics compared with healthy volunteers)	10 wk (1 mo treatment periods separated by 2-wk washout periods)	SPIRO 50 mg/d or placebo for 1 mo, then 2 wk washout, then 1 mo crossover	Significant increase with SPIRO in HbA_{1c} of 0.24 $\pm$0.08% ($P=.003$) and cortisol (508.9 [157.4] nmol/L vs placebo 455.8 [151.3] nmol/L; $P<.05$) No change in fasting glucose
Nielsen SE[42]	2012	Double-blind, randomized, placebo-controlled crossover study	21 patients with type I diabetes and microalbuminuria	4 mo (60 d each treatment period)	SPIRO 25 mg/d or placebo	Significant increase in HbA_{1c} with SPIRO from 8.2 $\pm$ 0.2 to 8.6 $\pm$ 0.2% ($P=.019$)
Rossing K[43]	2005	Randomized, double-blind, crossover study	21 patients with type II diabetes and nephropathy (20 patients completed)	16 wk (8 wk treatment periods)	SPIRO 25 mg/d for 8 wk or placebo for 8 wk	Slight but statistically significant increase from 7.8 $\pm$ 0.4 to 8.1 $\pm$ 0.3% (mean difference of 0.3; $P=.03$) in HbA_{1c}
Schjoedt KJ[44]	2005	Double-blind, randomized, crossover trial	20 patients with diabetes and macroalbuminuria	4 mo (2 mo treatment periods)	SPIRO 25 mg/d or placebo	Nonsignificant increase in HbA_{1c} from 8.4 (0.2) to 8.6 (0.2)%, mean difference 0.2 (−0.01 to 0.4) Worse effect with SPIRO ($P=.056$)
van den Meiracker AH[45]	2006	Placebo-controlled, double-blind, parallel group trial	59 patients with type II diabetes, macroalbuminuria, diagnosis of diabetic nephropathy (53 remained)	1 y	SPIRO 25 to 50 mg/d or placebo	Glycemic control not changed, average change in HbA_{1c} of 0.03 (−0.34 to 0.42)% with SPIRO, versus placebo 0.14 (−0.22 to 0.05)% (P value not given)
Oxlund CS[46]	2013	Investigator-initiated, prospective, randomized, double-blind, placebo controlled trial	119 patients with diabetes and resistant hypertension (112 completed study)	16 wk	SPIRO 25 mg (57 patients completed, HbA_{1c} analyzed for 61 patients) or placebo (55 patients completed, HbA_{1c} analyzed for 58 patients) added to previous triple antihypertensive treatment Uptitration to 50 mg if blood pressure not lowered	No change in HbA_{1c} ($P=.22$)
Schjoedt KJ[47]	2006	Randomized, double-blind, placebo-controlled, crossover trial	20 patients with type I or type II diabetes, diabetic nephropathy, hypertension	4 mo (2 mo treatment periods)	SPIRO 25 mg/d or placebo	No change in HbA_{1c} ($P=.20$)
Takebayashi K[48]	2006	Randomized, parallel-group	37 patients with type II diabetes and diabetic nephropathy (25 matched controls)	3 mo	SPIRO 50 mg/d (23 patients) or amlodipine (14 patients)	Significant increase in HbA_{1c} from 7.6 $\pm$ 1.4 to 8.2 $\pm$ 1.4% ($P=.0059$) with SPIRO, versus nonsignificant increase in comparator amlodipine 7.7 $\pm$ 1.8 to 7.5 $\pm$ 1.4% ($P=.702$) Difference between 2 groups $P=.0624$ No change in fasting plasma glucose ($P=.1859$)
Matsumoto S[49]	2006	Prospective, randomized	33 patients with diabetes, nephropathy, without clinically apparent symptoms of chronic HF	3 mo	SPIRO 50 mg/d or amlodipine	Significant increase in HbA_{1c} from 7.6 $\pm$ 1.4 to 8.2 $\pm$ 1.5% ($P=.0025$) and adiponectin only with SPIRO

(*continued*)

Table 4
(continued).

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
			(22 on SPIRO, 11 on amlodipine) Clinical characteristics of diabetic patients also compared with 25 healthy volunteers			No values reported for amlodipine or the comparison between groups No changes in fasting plasma glucose, insulin, or HOMA-IR
Mehdi UF[50]	2009	Prospective, randomized, double-blind, placebo-controlled trial	81 patients with diabetes, hypertension, and albuminuria (27 on SPIRO-17 patients completed)	48 wk	SPIRO 25 mg/d or placebo or losartan, with lisinopril	No change in HbA_{1c} Glucose levels fluctuated similarly in the groups Fasting glucose was lower at baseline in SPIRO group
Garg R[51]	2015	Double-blind, randomized, controlled study	69 randomized (64 patients completed) with type II diabetes	3 mo run-in phase with enalapril, 6 mo study	SPIRO 25 mg versus HCTZ 12.5 mg versus placebo	No significant changes between groups (SPIRO vs HCTZ glucose $P=.99$, HbA_{1c} $P=.94$; SPIRO vs HCTZ + placebo glucose $P=.52$, HbA_{1c} $P=.64$) SPIRO: change in HbA_{1c} $0.16 \pm 0.39\%$ and glucose 10.5 ± 23.9 mg/dL
Momeni A[52]	2015	Randomized, double-blind trial	60 patients with type II diabetes and nephropathy	3 mo	SPIRO 50 mg/d plus placebo versus SPIRO 50 mg/d plus HCTZ 25 mg/d versus HCTZ 25 mg/d plus placebo	SPIRO with placebo or SPIRO with HCTZ: no significant change in fasting blood sugar, 2-h post-prandial blood sugar, 5 PM blood sugar, or HbA_{1c} HCTZ with placebo: significant increase in fasting blood sugar compared to baseline No significant difference between groups
Viswanathan V[53]	2013	Randomized, open-label, placebo-controlled study	260 patients with type II diabetes (180 randomized)	24 wk (4-wk run-in period with rosiglitazone)	SPIRO 50 mg/d with rosiglitazone or amiloride with rosiglitazone or placebo with rosiglitazone	Improvement in HbA_{1c} in all 3 groups from 0.8 to 1% (due to the use of rosiglitazone in all groups) SPIRO: significant decrease in HbA_{1c} by 0.94 (1.6 to 0.27, $P=.008$)
Karalliedde J[54]	2006	Multicenter, open-label, randomized, parallel-group, proof of concept study	260 patients with type II diabetes	7 d (with previous 12-wk treatment with rosiglitazone), safety assessments for another 3 to 4 wk	Rosiglitazone with 50 mg SPIRO (but average 69 mg) versus rosiglitazone with furosemide versus rosiglitazone with HCTZ versus rosiglitazone alone versus withdrawal of rosiglitazone	No significant changes in glycemic control in any of the groups (fasting plasma glucose and HbA_{1c})
Davidson MB[55]	2008	Prospective, open-label trial, no randomization, no control group	24 patients with type II diabetes and albuminuria (11 with microalbuminuria and 13 with macroalbuminuria)	12 wk (initial observational 4 wk, 4 wk treatment with SPIRO, 4 wk follow-up without treatment)	SPIRO 25 mg/d	No changes in glucose throughout the duration of the study
Epstein M[56]	2006	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial	268 patients with diabetes (91 EPLE 50 mg, 86 EPLE 100 mg, 91 placebo)	12 wk of treatment (with a 2 to 4 wk open-label run-in period with enalapril)	EPLE 50 mg or 100 mg or placebo (with enalapril 20 mg/d)	No change in HbA_{1c}
Joffe HV[57]	2007	Randomized, double-blind crossover study	16 patients with diabetes, albuminuria, no clinical cardiovascular disease	16 wk (6 wk treatment periods separated by 4 wk washout)	EPLE 50 mg with placebo versus HCTZ with placebo for 6 wk, then 6 wk crossover (4 wk washout)	No change in HbA_{1c}, glucose or fructosamine

(*continued*)

Table 4
(continued).

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Karashima S[58]	2016	Randomized controlled trial	50 patients (25 per group; 45 patients completed the study, 23 in EPLE group and 22 in HCTZ group) with type II diabetes and essential hypertension	12 mo	EPLE 50 mg/d versus HCTZ (added to candesartan 8 mg)	EPLE: no significant effect on HbA_{1c}, fasting plasma glucose, HOMA-R, HOMA-β; significant increase in adiponectin (2.2 ± 0.3 to 2.6 ± 0.4 ng/mL; $P < .05$) HCTZ: significant increase in HbA_{1c} (6.36 ± 0.18 to 6.50 ± 0.20%) No significant difference between groups
Fogari R[59]	2014	Prospective, randomized, probably double-blind, parallel group study	120 patients with type II diabetes, hypertension and microalbuminuria	6 mo	Canrenone 25 mg versus HCTZ 12.5 mg (dose doubled if uncontrolled blood pressure), both added to valsartan plus amlodipine	No changes in fasting plasma glucose or HbA_{1c} in either group

EPLE = eplerenone, HbA_{1c} = glycated hemoglobin, HCTZ = hydrochlorothiazide, HF = heart failure, SPIRO = spironolactone.

studies evaluated the effect on glucose, insulin, HOMA-IR, fasting immunoreactive insulin (IRI), AUC insulin, AUC glucose, oral glucose tolerance test (OGTT), and insulin sensitivity indices.

Interestingly, SPIRO seemed to have a neutral or even a beneficial effect on glycemia in these patients, as opposed to other diseases where it had a tendency to exert a deleterious effect. In PCOS and hirsutism, it has been suggested that the favorable effect may be due to the decrease, and therefore the improvement, in the levels of testosterone, mediated by SPIRO.[74,76]

3.1.7. Hyperaldosteronism. Four articles were published on the effect of SPIRO in primary hyperaldosteronism (Table 7).[79–82] Three of these studies were prospective, without randomization.[79–81] Surgery or pharmacological treatment was chosen based on patients' needs. Patients with adenomas underwent adrenalectomy, while patients with idiopathic hyperaldosteronism were treated with SPIRO. The fourth study was a noninterventional cross-sectional study in which only SPIRO was used as a treatment.[82]

Sample sizes were rather small, ranging from 9 to 47 patients, and the follow-up varied between 6 months and 5.7 years. The doses of SPIRO were between 25 and 300 mg. HbA_{1c} was used as a biomarker in only 1 study,[79] and incidence of diabetes was not assessed in any of them. The other biomarkers in these studies included insulin, C-peptide, glucose, HOMA-IR, homeostatic model assessment of β-cell function (HOMA-βF), glucose disposal rate, insulin sensitivity index, metabolic clearance rate of glucose, OGTT, fasting insulin to glucose ratio, hyperinsulinemic-euglycemic clamp, AUC insulin, and AUC glucose.

The results on hyperaldosteronism varied, as the effects were different depending on the different biomarkers. Given the limited number of investigations and patients, no definitive conclusion can be made regarding this disease.

3.1.8. Other conditions. Finally, 4 studies were published on other diverse patient populations (Table 8). Two studies were performed on patients with kidney disease, including 1 RCT[83] and 1 sequential fixed-dose study.[84] One retrospective cohort study evaluated patients with hypertension and hepatitis C.[85] A fourth article presented preliminary results of an RCT on patients with nonalcoholic fatty liver disease.[86]

Sample sizes varied widely between 9 and 240 patients, and the duration of follow-up also differed from 8 weeks to 5.4 years. SPIRO was administered at doses of 25 to 50 mg. HbA_{1c} was not evaluated; however, incidence of diabetes was a measured biomarker. Other markers included glucose, insulin, HOMA-IR, and QUICKI. The results were inconclusive.

3.2. Meta-analysis

In most pathologies, few RCTs (between one and 3) evaluated the effect of SPIRO specifically on HbA_{1c}. There was a sufficient number of RCTs only in patients with diabetes (6 parallel-group trials and 6 crossover trials), where the majority of studies measured this specific marker. There were no RCTs that measured and reported the risk of diabetes. Consequently, overall, 2 meta-analyses were conducted on prospective RCTs with diabetic patients. The first quantitative analysis was performed on 6 parallel-group studies, and the second analysis included 6 crossover studies.

In the parallel-group studies (Fig. 2), the difference in mean of HbA_{1c} between SPIRO and the comparator group was nonsignificant (mean difference 0.03 [95% CI: −0.20 to 0.26]).

Table 5

Results for heart failure.

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Ogino K[60]	2014	Double-blind, randomized, controlled, crossover study	16 patients with chronic HF	32 wk (16-wk treatment periods with 4-wk washout period)	SPIRO 25 mg/d versus furosemide 20 mg/d	No change in fasting plasma glucose Improvement in fasting insulin (5.3 ± 0.5 to 2.8 ± 0.4 μU/mL, $P = .001$) and HOMA-IR (1.42 ± 0.17 to 0.71 ± 0.10, $P = .004$) with SPIRO, but not with furosemide (difference between groups: $P = .0001$ for insulin and $P = .0005$ for HOMA-IR)
Preiss D[61]	2009	Retrospective cohort study: substudy of CHARM	1620 nondiabetic patients with chronic HF	Median of 2.8 y	Candesartan or placebo	SPIRO not an independent predictor of incident diabetes; $P = .25$ in the multiple logistic regression model (significant in univariate logistic regression $P = .03$)
Preiss D[62]	2012	Substudy of EMPHASIS (randomized, double-blind, placebo-controlled trial)	1846 patients with systolic HF, without baseline diabetes (from 2737 EMPHASIS)	Maximum of 21 mo	EPLE up to 50 mg/d or placebo	No effect on onset of diabetes with EPLE
Ukena C[63]	2012	Substudy of EPHESUS study (multicenter, randomized, double blind trial)	6497 patients with acute myocardial infarction, LVEF $\leq 40\%$, clinical signs of HF (3262 EPLE and 3235 placebo)	Maximum mean range of follow-up 16 ± 7 mo	EPLE 25 to 50 mg or placebo	No significant interaction between EPLE and blood glucose levels regarding clinical outcomes
Yamaji M[64]	2010	Prospective, open-label, randomized Blinding not mentioned	107 patients with mild chronic HF, NYHA II-IV, HF (34 SPIRO, 73 EPLE)	4 mo	SPIRO 25 mg/d or EPLE 50 mg/d	SPIRO: significant increase in serum cortisol from 11.3 to 14.7 ($P = .003$) and HbA_{1c} from 5.6 to 5.8 ($P < .0001$); significant decrease in adiponectin ($P < .0001$) EPLE: no change observed Between groups: statistically significant difference in cortisol ($P = .003$), HbA_{1c} ($P = .0006$), and adiponectin ($P = .03$) Significant positive correlation between change in cortisol and change in HbA_{1c} with SPIRO ($P = .003$)

EPLE = eplerenone, HF = heart failure, HOMA-IR = homeostasis model assessment of insulin resistance, SPIRO = spironolactone.

Table 6

Results for PCOS and hirsutism.

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Ganie MA[65]	2013	Open-label, randomized study	198 women with PCOS (169 women completed)	6 mo	SPIRO 50 mg/d or metformin 500 mg twice/d or combination	SPIRO alone: significant decrease in post-OGTT glucose and area-under-curve glucose; significant change in plasma insulin and OGTT-derived insulin sensitivity indices Combination SPIRO with metformin: superior improvement
Vieira CS[66]	2012	Randomized, controlled, open-label clinical trial	50 women (then 41) with PCOS	12 mo	SPIRO 100 mg/d with OC (2 mg chlormadinone and 30 μg ethinylestradiol) versus OC alone	3% reduction in mean glucose with SPIRO ($P=.01$), no change in other parameters (insulin and HOMA-IR) OC: 5% decrease in mean glucose ($P<.01$) No significant difference between groups
Mazza A[67]	2014	Prospective randomized study	56 overweight or obese patients with PCOS	6 mo	SPIRO 25 mg/d with metformin 1700 mg/d and hypocaloric diet versus metformin 1700 mg/d alone with hypocaloric diet	Fasting glucose, serum insulin, and HOMA-IR index values significantly decreased in both groups ($P<.001$) Nonsignificant difference between groups (except significant difference 120' glucose between groups $P<.001$)
Kebapcilar L[68]	2010	Randomized	48 women with PCOS (12 with SPIRO)	3 mo	SPIRO 100 mg/d with ethinylestradiol plus cyproterone acetate (EE/CA) versus EE/CA alone versus EE/CA with metformin versus metformin	Significant reduction in insulin from 22.3 ± 6.1 to 19.8 ± 5.2 ($P=.002$) and HOMA-IR from 4.6 ± 1.4 to 4.0 ± 1.2 ($P=.002$) with combination SPIRO and EE/CA In all groups (EE/CA-metformin more effective therapeutic option, may be due to beneficial effect on IR-significant decrease)
Diri H[69]	2016	Randomized controlled trial	37 women with PCOS (18 patients on SPIRO alone, 19 patients on combination therapy)	12 mo	SPIRO 100 mg/d versus SPIRO 100 mg/d with metformin 2000 mg/d (SPIRO titrated in the first week from a starting dose of 50 mg/d in both groups)	SPIRO alone: nonsignificant decrease in HOMA-IR (1.09 ± 0.2 to 1.01 ± 0.2) No significant difference between groups in HOMA-IR
Kebapcilar L[70]	2010	Randomized	56 women with PCOS (28 with SPIRO)	3 mo	SPIRO 100 mg/d with EE/CA versus EE/CA	Significant reduction in insulin from 19.7 ± 4.8 to 17.9 ± 4.0 μIU/mL ($P=.001$) and HOMA-IR from 3.8 ± 1.2 to 3.4 ± 1.0 with combination SPIRO and EE/CA Significant reduction in insulin and HOMA-IR also with EE/CA alone ($P<.001$)
Meyer C[71]	2007	Open-label controlled trial	100 overweight women with PCOS (33 on SPIRO, 31 on high dose OC, 36 on metformin)	6 mo	SPIRO 50 mg b.d. with OC or metformin or high dose OC	No change in insulin resistance with SPIRO Insulin resistance improved with metformin; high dose OC: AUC insulin increased
Studen KB[72]	2011	Prospective, no control group	30 nonobese patients with PCOS and 20 controls	6 mo (21 d treatment, 7 d pause) for PCOS patients	SPIRO 100 mg/d	No change in HOMA-IR before and after treatment
Nakhjavani M[73]	2009	Prospective, no control group	27 patients with hirsutism enrolled (20 with PCOS and 7 with idiopathic hirsutism) Initially 53 recruited	3 mo	SPIRO average 100 mg/d	No significant change in glucose
Shoupe D[74]	1984	Prospective, no control group (spironolactone not compared to any comparator)	14 patients with idiopathic hirsutism IH (all on SPIRO), 13 patients with PCOS (5 on SPIRO), 6 healthy controls	2 wk	SPIRO 100 mg/d (all IH patients and 5 PCOS patients)	IH: no effect on IRI or T PCOS: significantly lowered T and IRI IRI: 20.0 ± 2.2 to 11.2 ± 2.0 with SPIRO in PCOS ($P<.05$ compared with baseline)

(*continued*)

Table 6
(continued).

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Zulian E[75]	2005	Prospective clinical trial, no control group (only addition of diet to overweight patients)	25 patients with PCOS	12 mo	SPIRO 100 mg/d and food restriction	Improvement observed in women with food restriction and weight loss (insulin at 60 min after 75 g glucose load, HOMA-IR, AUC insulin), and no negative long-term effect observed (since there is no control group, improvement is probably due to weight loss, not SPIRO)
Moghetti P[76]	1996	Prospective, different medication prescribed based on patient's symptoms	43 women with hyperandrogenism (hirsutism and/or PCOS), and 12 healthy controls	3 to 4 mo (6 patients on SPIRO reexamined after 1 y)	SPIRO 100 mg/d or flutamide or buserlin	No change in plasma glucose or insulin with SPIRO Improvement in insulin sensitivity: insulin resistance improved by 63.3 and 43.2% at low and high insulin infusion rates, respectively Not statistically significant in overweight patients (obesity determines insulin resistance) Increase in insulin sensitivity regardless of drug
Wild RA[77]	1991	Prospective, assigned to treatment based on contraceptive need	51 women with hirsutism	9 mo (evaluate at baseline, 3 mo, and 9 mo)	SPIRO 200 mg/d or OCs (ethinylestradiol 35 μg with norethindrone 0.4 mg or ethinylestradiol 30 μg with norethindrone acetate 1.5 mg)	Increase in fasting insulin with SPIRO ($P < .05$) in Figure 2 No effect with comparator
Kulshreshta B[78]	2012	Retrospective, observational analysis	88 patients with PCOS (46 on SPIRO, 13 with AGT)	6 mo	SPIRO 50 to 75 mg/d or metformin	*SPIRO:* *Pre-OGTT:* Nonsignificant increase in insulin: 13.1 ± 11.4 to 18.3 ± 23.7 ($P = .07$) No significant change in glucose ($P = .97$) Borderline increase in HOMA-IR: 3.1 ± 3.4 to 4.3 ± 6.0 ($P = .088$) *Post-OGTT:* Significant reduction in 2-h insulin: 85.9 ± 104.0 to 69.0 ± 81.7 ($P = .02$) *Metformin:* *Pre-OGTT:* Significant decrease in insulin: 17.7 ± 16.8 to 11.0 ± 6.3 ($P = .042$) No significant change in glucose ($P = .17$) Significant decrease in HOMA-IR: 3.8 ± 3.3 to 2.5 ± 1.3 ($P = .04$) *Post-OGTT:* Significant decrease in 2-h glucose (135.9 ± 47.6 to 121.9 ± 42.3 mg/dL, $P = .008$), 1-h insulin (155.9 ± 102.4 to 74.9 ± 63.1, $P = .00$), and 2-h insulin (97.2 ± 60.9 to 61.4 ± 79.3, $P = .01$)

AGT = abnormal glucose tolerance, AUC = area under curve, HOMA-IR = homeostasis model assessment of insulin resistance, IH = idiopathic hirsutism, IRI = fasting immunoreactive insulin, NGT = normal glucose tolerance, OC = oral contraceptive, OGTT = oral glucose tolerance test, PCOS = polycystic ovary syndrome, SPIRO = spironolactone, T = testosterone.

Table 7

Results for hyperaldosteronism.

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Sindelka G[79]	2000	Prospective	9 patients with primary hyperaldosteronism (5 patients with aldosterone producing adenoma and 4 patients with idiopathic hyperaldosteronism and bilateral hyperplasia) Healthy controls matched by age and BMI for each group	6 mo	SPIRO 100 to 150 mg/d for the 4 patients with idiopathic hyperaldosteronism Unilateral adrenalectomy for the 5 patients with aldosterone producing adenoma	SPIRO: Slight increase in HbA_{1c} ($P<.05$) Worsening in insulin action (glucose disposal rate, insulin sensitivity index, metabolic clearance rate of glucose) Adrenalectomy: improvement in insulin action
Strauch B[80]	2003	Prospective, no randomization	24 patients with primary hyperaldosteronism (APA or IHA, 11 with IHA on SPIRO)	Mean follow-up of 3.6 y	SPIRO 50 to 75 mg/d (IHA patients) or adrenalectomy (APA patients)	Slight increase in plasma glucose during total glucose tolerance test (OGTT), may be explained by higher BMI in the IHA group APA (surgery): no improvement in glucose levels
Catena C[81]	2006	Prospective study with follow-up, parallel	47 patients with aldosteronism (27 SPIRO: 5 had adrenal adenomas, 22 had idiopathic aldosteronism), 247 patients with essential hypertension, 102 normotensive patients (tumoral or idiopathic) primary aldosteronism	Average follow-up of 5.7 y	SPIRO 50 to 300 mg/d or surgical treatment (unilateral adrenalectomy)	6 mo: restored to normal, but long-term follow-up: nonsignificant changes in glucose metabolism (no further change) (Glucose, insulin, C-peptide, fasting insulin to glucose ratio, hyperinsulinemic-euglycemic clamp (20 patients), OGTT, AUC glucose and insulin)
Mosso LM[82]	2007	Non interventional, cross-sectional	30 patients with PA (19 PA on SPIRO) and 60 patients with EH (controls)	6 mo	SPIRO 25 mg/d, dose increased until PRA and blood pressure normalized	Increase in insulin from 8.68 ± 5.33 to 13.39 ± 6.66 ($P=.048$) and C-peptide from 0.82 ± 0.57 to 3.32 ± 1.24 ($P<.001$), no changes in glucose, HOMA-IR or HOMA-βF

APA = aldosterone producing adenoma, AUC = area under curve, BMI = body mass index, EH = essential hypertension, HbA_{1c} = glycated hemoglobin, HOMA-βF = homeostatic model assessment of β-cell function, HOMA-IR = homeostasis model assessment of insulin resistance, IHA = idiopathic hyperaldosteronism, OGTT = oral glucose tolerance test, PA = primary aldosteronism, PRA = plasma renin activity, SPIRO = spironolactone.

Table 8

Results for other conditions.

Author	Year	Study design	Patients disease	Follow-up	Medication dose	Results of markers
Hosoya K[83]	2015	Prospective, randomized, placebo-controlled	24 patients with chronic kidney disease	6 mo	SPIRO 25 mg/d or placebo	Significant decrease in HOMA-IR and fasting insulin with SPIRO versus control group: % change HOMA-IR control 29.0±13.1 versus SPIRO −53.7±6.5, $P<.01$ % change fasting insulin control 25.7±11.7 versus SPIRO −51.2±7.1, $P<.01$
Michea L[84]	2004	Sequential, fixed-dose, probably double-blind, single-center study	9 patients with anuria and hemodialysis	8 wk (2 wk pre-drug period, 2 wk SPIRO, 2 wk washout, 2 wk placebo)	SPIRO 50 mg or placebo 3 times/wk Potassium-carbohydrate load at pre-drug and end of each period	No significant difference between the 3 phases in plasma glucose or insulin, before and after potassium-carbohydrate load
Arase Y[85]	2009	Retrospective cohort study	240 patients with hypertension, hepatitis C virus, chronic liver disease (80 on losartan and 160 on SPIRO as controls)	Mean of 5.4 y	SPIRO 25 or 50 mg/d (control group) or losartan	Greater onset of T2DM with SPIRO: 14.4% rate versus 5.4% with losartan ($P=.025$)
Polyzos SA[86]	2011	Preliminary results of a single-centered randomized controlled trial Parallel	20 patients with nonalcoholic fatty liver disease (10 on SPIRO with vitamin E)	52 wk planned (interim analysis at 8 wk)	SPIRO 25 mg/d with vitamin E or vitamin E alone	SPIRO with vitamin E: No difference in glucose Favorable effect on insulin 15.3±2.7 to 10.3±1.6 ($P<.05$) and HOMA-IR 4.4±0.9 to 2.8±0.5 ($P<.05$) Nonsignificant increase in QUICKI Vitamin E alone: no change, or positive nonsignificant change

HOMA-IR = homeostasis model assessment of insulin resistance, QUICKI = quantitative insulin sensitivity check index, SPIRO = spironolactone, T2DM = type 2 diabetes mellitus.

Table 9

Summary of results.

Health condition	Results
Healthy volunteers	Few studies: 2 prospective studies • 1 on spironolactone (no randomization reported) • 1 on eplerenone (no control group) Small sample sizes: 13 to 18 patients Short duration: 10 to 14 d Doses: 100 mg spironolactone, 50 mg eplerenone Measured biomarkers: glucose, insulin, HOMA-IR (HbA_{1c} or diabetes not evaluated) Results: spironolactone and eplerenone exert a neutral effect
Hypertension	Multiple studies (14): • 11 studies with spironolactone (7 RCTs, 1 prospective nonrandomized without controls, 3 observational) • 3 studies with eplerenone (1 RCT, 2 prospective without control groups) Varied sample sizes: 15 to 1141 patients Varied duration: 2 mo to 10 y Doses: spironolactone 25 to 100 mg (except one study with 200 mg and another study with 400 mg), eplerenone 25 to 50 mg Measured biomarkers: glucose, insulin, AUC glucose, AUC insulin, HOMA-IR, QUICKI, HbA_{1c} (only in 3 studies) Results: • Spironolactone: heterogeneous ○ Negative or slightly negative versus placebo or no comparator ○ More positive on glycemia versus chlorthalidone ○ Inconclusive in studies with hydrochlorothiazide or trichlormethiazide ○ No significant effect in comparison to perindopril or placebo • Eplerenone: neutral
Obesity/metabolic syndrome	Limited number of studies (9): • 2 RCTs on obese patients evaluating spironolactone • 7 studies on patients with metabolic syndrome ○ 3 spironolactone (1 RCT, 1 prospective nonrandomized, 1 prospective without control group) ○ 1 RCT on eplerenone versus spironolactone ○ 1 placebo-controlled RCT on eplerenone ○ 2 placebo-controlled trials on canrenone (not randomized) Average sample sizes: 8 to 156 patients Average duration: 1 mo (crossover) to 9 mo Doses: spironolactone 25 to 75 mg, eplerenone 25 to 100 mg, canrenone 50 to 100 mg Measured biomarkers: glucose, insulin, HOMA-IR, AUC glucose, AUC insulin, insulin sensitivity index, glucose effectiveness, IV glucose tolerance Results: • Spironolactone: no negative effect • Eplerenone: no effect • Canrenone: potentially beneficial effect
Diabetes	Multiple studies: 20 studies • 16 studies on spironolactone (15 RCTs, 1 prospective no controls) • 3 RCTs on eplerenone • 1 RCT on canrenone Average sample sizes: 16 to 268 patients Average duration: 8 wk to 1 y (except 1 study: 1-wk treatment) Doses: spironolactone 25 to 50 mg, eplerenone 50 to 100 mg, canrenone 25 mg Measured biomarkers: HbA_{1c} (in 18 studies), cortisol, glucose, insulin, HOMA-IR, HOMA-β, adiponectin, fructosamine Results: • Spironolactone: significantly negative (6 studies) or nonsignificant negative (3 studies) effect on glycemia • Eplerenone: neutral effect (and significant increase in adiponectin) • Canrenone: potentially neutral effect Meta-analysis on spironolactone: • 6 parallel-group studies: no significant effect on HbA_{1c} • 6 crossover studies: significantly negative effect on HbA_{1c} (increase)
Heart failure	Limited number of studies: 5 studies • 2 studies on spironolactone (1 RCT, 1 retrospective cohort study) • 2 substudies of large RCTs on eplerenone • 1 RCT on eplerenone versus spironolactone Greater sample sizes: 107 to 6497 patients (except 1 study with 16 patients) Varied duration: 4 mo to 2.8 y Doses: spironolactone 25 mg, eplerenone 25 to 50 mg Measured biomarkers: glucose, insulin, HOMA-IR, incidence of diabetes, cortisol, adiponectin, HbA_{1c} (1 study) Results:

(*continued*)

Table 9

(continued).

Health condition	Results
	• Spironolactone: deleterious effect on glycemia through an increase in cortisol • Eplerenone: neutral effect
PCOS/hirsutism	Multiple studies: 14 studies on spironolactone • 7 RCTs • 4 prospective no controls • 2 prospective, medication assigned based on patients' needs • 1 observational Limited to average sample sizes: 14 to 100 patients (except in 1 study 198 patients) Limited to average duration: 2 wk to 12 mo Doses: 50 to 200 mg (usually higher than in other diseases) Measured biomarkers: glucose, insulin, HOMA-IR, IRI, AUC insulin, AUC glucose, OGTT, insulin sensitivity indices (HbA_{1c} or diabetes not evaluated) Results: • Spironolactone: neutral or even beneficial effect on glycemia • May be potentially due to decrease in abnormally high testosterone levels
Hyperaldosteronism	Few studies: 4 studies on spironolactone • 3 prospective (no randomization—surgery or pharmacological treatment based on patients' needs) • 1 noninterventional cross-sectional study, no comparator Small sample sizes: 9 to 47 patients Varied duration: 6 mo to 5.7 y Doses: spironolactone 25 to 300 mg Measured biomarkers: insulin, C-peptide, glucose, HOMA-IR, HOMA-βF, glucose disposal rate, insulin sensitivity index, metabolic clearance rate of glucose, OGTT, fasting insulin to glucose ratio, hyperinsulinemic-euglycemic clamp, AUC insulin, AUC glucose, HbA_{1c} (1 study) Results: • Inconclusive results • Different effects on different biomarkers
Other conditions	Few studies on spironolactone: • 2 studies in kidney disease (1 RCT, 1 sequential fixed-dose study) • 1 retrospective cohort study on patients with hypertension and hepatitis C virus • 1 study on patient with nonalcoholic fatty liver disease (preliminary results of RCT) Varied sample sizes: 9 to 240 patients Varied duration: 8 wk to 5.4 y Doses: spironolactone 25 to 50 mg Measured biomarkers: glucose, insulin, HOMA-IR, incidence of diabetes, QUICKI Results: inconclusive

AUC = area under the curve, HbA_{1c} = glycated hemoglobin, HOMA-βF = homeostatic model assessment of β-cell function, HOMA-IR = homeostasis model assessment of insulin resistance, IRI = immunoreactive insulin, OGTT = oral glucose tolerance test, PCOS = polycystic ovary syndrome, QUICKI = quantitative insulin sensitivity check index, RCT = randomized controlled trial.

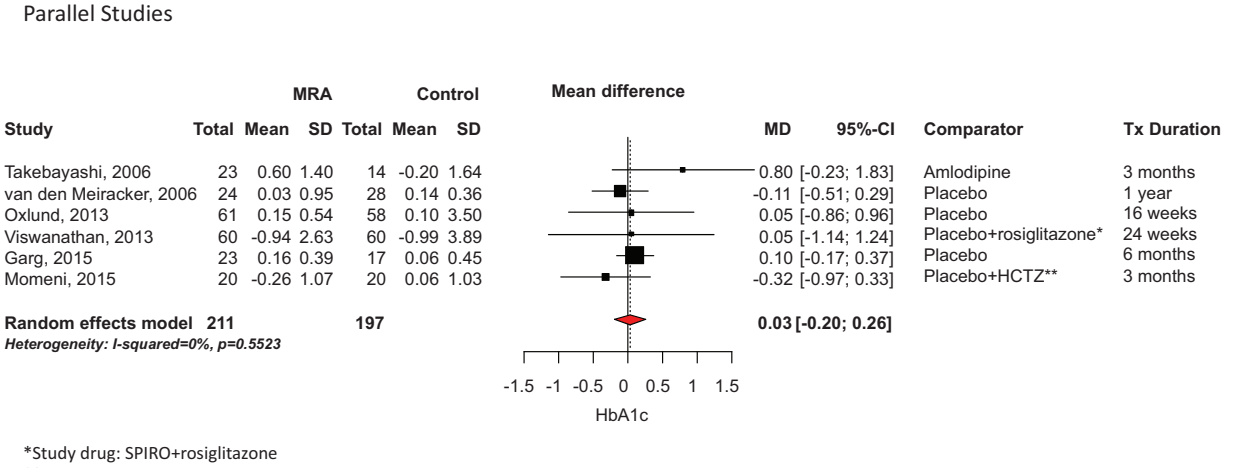

Figure 2. Meta-analysis of parallel-group studies.

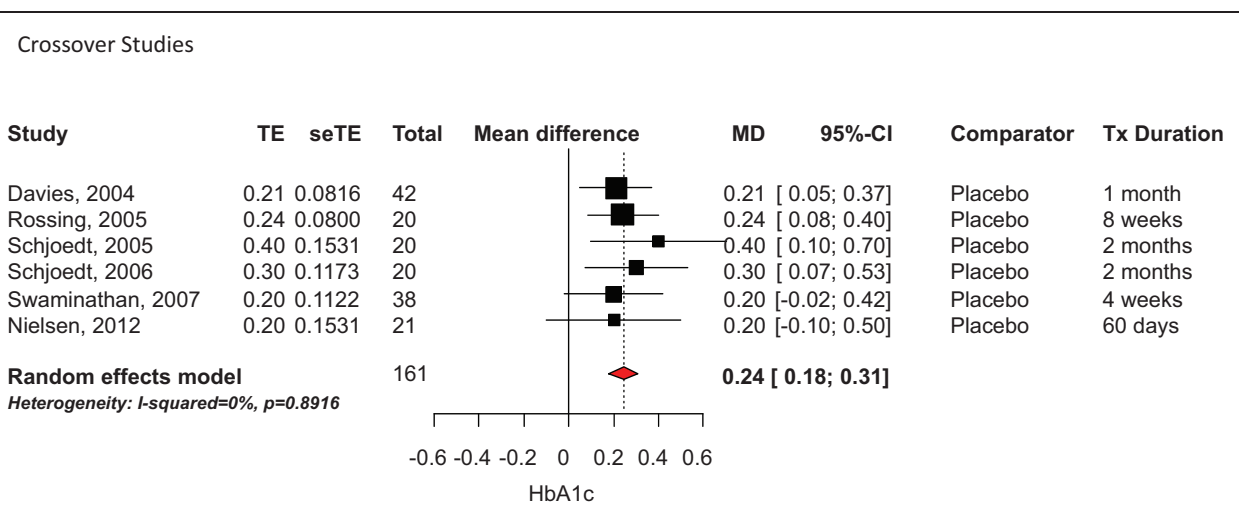

Figure 3. Meta-analysis of crossover studies.

However, a significant difference in mean was observed in the crossover studies (mean difference 0.24 [95% CI: 0.18–0.31]; Fig. 3). There was no indication of heterogeneity in either one of the meta-analyses ($I^2 = 0\%$).

4. Discussion

4.1. Summary

Overall, the multiple studies conducted on SPIRO yielded heterogeneous results. These differences may be due in part to the small sample sizes in many of the studies, heterogeneous study designs and medical conditions, as well as the variability in the glycemic markers that were evaluated. However, certain trends are apparent when summarizing the impact of SPIRO in some distinct health conditions (Table 9), suggesting that SPIRO's effect may be disease-specific. On the other hand, our review confirms that EPLE does not have an impact on glucose homeostasis in any of the diseases that were studied. The very few investigations on canrenone suggest that it exerts a neutral or a beneficial effect.

According to our review, SPIRO may have an adverse effect in diabetes and HF. It does not seem to have a significant impact on glucose levels in the metabolic syndrome or hyperaldosteronism. On the other hand, it may either have a neutral or even a beneficial effect on glucose metabolism in diseases characterized by hyperandrogenism. Results from studies performed on healthy individuals, as well as in those on patients with hypertension, were inconclusive. These observations may also be related to the fact that HbA_{1c}, a more sensitive biomarker of long-term glycemic control, was primarily measured in studies with HF and diabetic patients. This marker was used in very few studies on patients with other diseases. In investigations that found a negative effect on HbA_{1c}, the average increase was, mostly, between 0.2% and 0.3%. The long-term effects of such increases in HbA_{1c} remain largely unknown. However, such increases may have significant long-term clinical consequences as a 1% increase in HbA_{1c} translates into a 15% increase in all-cause mortality and 25% increase in CV mortality in patients with diabetes.[89] Overall, we may observe that SPIRO seems to exert a moderately negative effect on glucose regulation in patients who suffer from CV diseases or who have illnesses that increase the risk of developing heart disease, such as diabetes. On the other hand, SPIRO seems to exert a potentially favorable effect on non-CV hormonal diseases, such as PCOS.

4.2. Meta-analysis

Results from the meta-analyses with SPIRO are ambiguous, as they were nonsignificant in the parallel-group analysis, but significant in the crossover studies. The most distinguishable difference between these 2 sets of studies was the duration of treatment. The parallel-group studies had minimum treatment duration of 3 months, while the crossover studies had a maximum treatment phase of 2 months. We postulate that perhaps this contrast in the duration of follow-up may have contributed to these conflicting results. Indeed, diabetic patients that undergo a longer duration of treatment, such as the participants in the parallel-group trials, may be more likely to have their hypoglycemic agents adjusted if their glucose control worsens during the study. As such, if SPIRO did exert a significantly harmful effect on glycemia, it may have been masked by an adjustment of the patient's antidiabetic medication that is used to improve glucose metabolism. In the absence of large studies investigating the risk of diabetes, this explanation remains speculative. Additionally, there were fewer studies that used a placebo for the comparator group in the parallel-group studies. Some comparators, such as hydrochlorothiazide, are known to have a harmful impact on glycemia. However, these differences in the choice of comparator did not lead to any heterogeneity in study results. Therefore, this difference is probably not a significant limitation. Finally, SPIRO's effect on glucose homeostasis may simply be transient. Further research is required to explain these results, but the meta-analyses that were conducted confirm that if any deleterious effect exists, it would be modest.

A recent, systematic review and meta-analysis of randomized placebo-controlled trials, regarding SPIRO's glycemic effects, was conducted by Zhao et al.[95] From 18 RCTs, 8 studies provided information on the change in HbA_{1c}. We included 12 studies into our meta-analysis. The additional 4 studies in our analysis consisted of 2 RCTs with an active comparator rather than a placebo (exclusion criteria for Zhao et al),[48,52] as well as 2 studies that could have potentially been included into their

meta-analysis.[44,46] In the meta-analysis of these studies, SPIRO was associated with a significant increase in HbA_{1c} levels (mean difference 0.16; 95% confidence interval 0.02–0.30). SPIRO's impact on glucose, insulin, and HOMA-IR was nonsignificant. The value of HbA_{1c} was slightly lower but in a similar range to the numeric value that we found in our crossover studies (0.24; 95% CI 0.18–0.31). However, the authors pooled parallel-group and crossover studies into a single analysis. In fact, in their meta-analysis, when crossover studies were excluded in their sensitivity analyses, the difference in HbA_{1c} was much smaller, not statistically significant (0.05; 95% CI −0.14 to 0.25), and very similar to our results computed from pooled parallel-group studies (0.03; 95% CI −0.20 to 0.26). Additionally, when the authors pooled 3 studies on HbA_{1c} that had a minimum duration of 3 months (all parallel-group studies), the estimate, once again, was small and nonsignificant (0.05; 95% CI −0.14 to 0.25). This observation is consistent with our own findings, where SPIRO did not have an effect on parallel-group studies with a longer duration of treatment. Zhao et al suggest that perhaps SPIRO's effect on glycemia is short-term, and does not persist on a long-term basis. This transient effect may also explain these results. The investigators also mention the possibility that SPIRO's anti-androgen effect may play a role in its impact on glucose control. The results that we obtained from the studies on patients with PCOS (not included in Zhao et al's paper) are in agreement with this hypothesis and potentially validate their assumptions. Overall, as we included more studies into our review, as well as into our meta-analysis of papers on HbA_{1c}, our paper provides complementary and supportive information to the earlier report by Zhao et al.

4.3. Potential mechanisms of action

A number of mechanisms have been proposed to explain SPIRO's effects on glucose sensitivity. Given the positive correlation between the increase in HbA_{1c} and the increase in cortisol, this glucocorticoid has been central to many hypotheses.[64] SPIRO's off-target effect on glucocorticoid receptors could lead to a reflex increase in cortisol,[64] a key player in glucose homeostasis through lipolysis and gluconeogenesis. Therefore, excess cortisol could potentially have a deleterious effect on glucose metabolism. Furthermore, cortisol has a similar affinity to the mineralocorticoid receptor as aldosterone.[96] The 11β-hydroxysteroid dehydrogenase type II (11β-HSDII) enzyme regulates cortisol levels and its activity through a conversion of this steroid to its inactive form (cortisone).[97] This transformation prevents cortisol from exerting additional effects and allows aldosterone to bind to its receptor. However, this enzyme is expressed at lower levels in skeletal muscle, liver, and adipose tissue.[96] Consequently, these tissues may be more sensitive to high levels of this glucocorticoid.

Others have suggested that mineralocorticoid receptor blockade itself could lead to cortisol accumulation through a reduction in clearance[40] or an inhibition of the negative feedback on the hypothalamo-pituatary axis.[98] Another hypothesis is that the increase in HbA_{1c} may be due to a compensatory increase in aldosterone, as the non-genomic mineralocorticoid receptors are not blocked.[42] Nevertheless, such hypotheses are not consistent with the lack of impact that EPLE has on glucose homeostasis. Indeed, it would be difficult to understand why the selective antagonist, EPLE, that exerts its effect on the same mineralocorticoid receptor, would not have a negative impact on glucose control. On the whole, more research is needed to establish the exact mechanisms by which cortisol may exert these effects.

These mechanisms can be responsible for the fact that the effects differ according to different diseases. The increase in cortisol by SPIRO could have a detrimental effect on glucose tolerance in diseases that already have increased baseline levels of this hormone and are related to CV disease, such as metabolic syndrome,[99] diabetes,[100] hypertension,[101] and HF.[102] This hypothesis is supported by a high rate of diabetes in the Cushing syndrome, a disease characterized by cortisol excess.[103]

The off-target anti-androgen effect of SPIRO may also play a role in modulating glycemia, because testosterone levels affect glucose homeostasis.[76] SPIRO's anti-androgenic effect may be either harmful or beneficial to glucose regulation, depending on the disease. In conditions that are characterized by hyperandrogenism, such as PCOS, the high baseline levels of testosterone may be linked to a risk of insulin resistance or even diabetes, and a decrease in this hormone during treatment with SPIRO may exert a beneficial effect on glucose tolerance.[74,76] On the contrary, circulating levels of testosterone are decreased in disorders related to CV disease, such as HF[104,105] and diabetes.[106] It has been suggested that low levels of testosterone could also be associated with insulin resistance[107]; consequently, the decrease in this hormone, mediated by the use of SPIRO, may result in an unfavorable milieu for glucose homeostasis. Overall, the use of SPIRO could tip the scale from risk to benefit, and vice-versa, depending on the baseline testosterone levels in each disease.

In contrast to SPIRO, current knowledge suggests that EPLE's selectivity may explain its neutral effect on glycemia. Similarly, canrenone's neutral or even beneficial effect on glucose control is possibly due to its more selective nature than its parent molecule SPIRO. Indeed, it has a decreased affinity for the androgen receptor in comparison to SPIRO.[93] However, it is not possible to draw any conclusions on canrenone from such a small number of studies.

4.4. Study limitations

Our review has important limitations. Regarding the limits of individual studies, many used designs prone to bias, such as retrospective or observational designs (see Table, Supplemental Content, illustrating study limits, http://links.lww.com/MD/B966). For our review, one of the most important biases from an observational study would be confounding by indication. Indeed, the prescription of an MRA may depend on the severity of the disease. If MRA users were sicker than nonusers, the effect observed on glycemia may have been related to disease severity rather than exposure to an MRA. This bias could overestimate the potential association between MRA exposure and glucose metabolism. Second, retrospective observational studies may not always include all of the important clinical variables that could be measured in RCTs, leading to differential and non-differential bias. In addition, confounders that require detailed information on clinical parameters and lifestyle were not measured in many studies, causing residual confounding bias. Confusion bias may also exist when the variable is associated with the exposure and outcome.

Among prospective studies, certain methodological choices may have also predisposed the studies to bias. For instance, some of these studies were nonrandomized. Rather, the prescription of an MRA was based on the patient's personal needs, symptoms, or disease etiology. Such study designs could lead to a selection bias. Also, certain prospective studies were not blinded. In such cases, analyses could potentially be influenced by the knowledge of the

treatment group. Furthermore, the lack of a washout period in some prospective trials may have generated a carryover effect.

Additionally, a number of articles had an incomplete description of the study design. This limited our capacity of assessing the quality of these studies. Moreover, the strength of evidence of studies was often weak because most studies had a short follow-up period, a small sample size, and/or markers that are not associated with long-term glucose metabolism (HbA_{1c} or development of diabetes). Many studies used comparator drugs that are known to have a positive or negative effect on glycemia, leading to possible overestimation or underestimation of MRAs' harmful glycemic effects, respectively. Nevertheless, this method did not induce heterogeneity, at least in our meta-analysis. Other studies did not have a control group. Also, some results were inconsistent within a study, as different glycemic markers had apparently opposite effects. Finally, in several articles, published results came from post-hoc analyses.

With respect to the limitations of the review process, the studies were quite different in terms of study design, study population, duration of treatment, doses, comparator medication, and types of glycemic markers. Few studies measured the effect on HbA_{1c} in most diseases, with the exception of diabetes. This restricted the number of studies that we could include into the meta-analysis. In addition, there were a limited number of studies, and even fewer RCTs, in diseases such as metabolic syndrome, HF, and hyperaldosteronism, preventing us from drawing conclusions about the effects of MRAs in these patients. Also, as some studies were conducted by the same groups, there was some overlap between study populations.[48,49] Moreover, the use of a single database may have slightly limited the number of selected articles. Although Medline is a comprehensive database of scientific publications, a second search engine may have provided additional relevant articles. Finally, only published articles were reviewed, leading to a potential publication bias. In general, studies that fail to reject the null hypothesis are less likely to be published. In our review, the absence of these studies may have resulted in an overestimation of MRAs' glycemic effects. Furthermore, if effects on glucose control were not part of the primary or secondary endpoints, some authors may have failed to report the effect that was measured on glycemia in their papers, as glucose markers are routinely measured in RCTs or observational studies. This may create an outcome reporting bias. As such, it is possible that certain studies found a significant association between an MRA and glucose homeostasis, but were not published because this variable was not part of their primary endpoint and the effect on their main outcome of interest was not significant. Although less likely, this publication bias may induce an underestimation of MRAs' glycemic effects.

5. Conclusion

The results of this systematic review indicate that different studies reported different effects of SPIRO on glucose homeostasis. Although these effects could be disease-specific, the inconsistencies between the studies and the limited quality of the study designs prevent us from drawing any definitive conclusions. Even within certain diseases, results were heterogeneous. Current evidence indicates that if spironolactone has any deleterious impact on glucose homeostasis, it is likely to be modest, and perhaps transient. On the other hand, EPLE, a selective MRA, does not appear to have an effect on glycemia in any of the diseases. Similarly, canrenone, a metabolite of SPIRO, seems to have a neutral or even positive effect. In the future, further investigations will be necessary to understand whether these potential pharmacological differences are clinically significant in terms of the long-term risk of diabetes or other clinically relevant outcomes.

References

[1] Pacurari M, Kafoury R, Tchounwou PB, et al. The Renin-Angiotensin-aldosterone system in vascular inflammation and remodeling. Int J Inflam 2014;2014:689360.

[2] Vongpatanasin W. Resistant hypertension: a review of diagnosis and management. JAMA 2014;311:2216–24.

[3] Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.

[4] Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364: 11–21.

[5] Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.

[6] Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.

[7] Harvey AM. Hyperaldosteronism: diagnosis, lateralization, and treatment. Surg Clin North Am 2014;94:643–56.

[8] O'Brien JG, Chennubhotla SA, Chennubhotla RV. Treatment of edema. Am Fam Physician 2005;71:2111–7.

[9] Mosenkis A, Townsend RR. Gynecomastia and antihypertensive therapy. J Clin Hypertens 2004;6:469–70.

[10] Prisant LM, Chin E. Gynecomastia and hypertension. J Clin Hypertens 2005;7:245–8.

[11] Satoh T, Munakata H, Fujita K, et al. Studies on the interactions between drug and estrogen. II. On the inhibitory effect of 29 drugs reported to induce gynecomastia on the oxidation of estradiol at C-2 or C-17. Biol Pharma Bull 2003;26:695–700.

[12] Giagulli VA, Moghetti P, Kaufman JM, et al. Managing erectile dysfunction in heart failure. Endocr Metab Immune Disord Drug Targets 2013;13:125–34.

[13] Somani N, Turvy D. Hirsutism: an evidence-based treatment update. Am J Clin Dermatol 2014;15:247–66.

[14] Goodman NF, Cobin RH, Futterweit W, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and Pcos Society Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome—Part 1. Endocr Pract 2015;21:1291–300.

[15] Clore JN, Estep H, Ross-Clunis H, et al. Adrenocorticotropin and cortisol-induced changes in urinary sodium and potassium excretion in man: effects of spironolactone and RU486. J Clin Endocrinol Metab 1988;67:824–31.

[16] Krug AW, Stelzner L, Rao AD, et al. Effect of low dose mineralocorticoid receptor antagonist eplerenone on glucose and lipid metabolism in healthy adult males. Metabolism 2013;62:386–91.

[17] Schersten B, Thulin T, Kuylenstierna J, et al. Clinical and biochemical effects of spironolactone administered once daily in primary hypertension. Multicenter Sweden study. Hypertension 1980;2:672–9.

[18] Plouin PF, Battaglia C, Alhenc-Gelas F, et al. Are angiotensin converting enzyme inhibition and aldosterone antagonism equivalent in hypertensive patients over fifty? Am J Hypertens 1991;4(part 1): 356–62.

[19] Raheja P, Price A, Wang Z, et al. Spironolactone prevents chlorthalidone-induced sympathetic activation and insulin resistance in hypertensive patients. Hypertension 2012;60:319–25.

[20] Menon DV, Arbique D, Wang Z, et al. Differential effects of chlorthalidone versus spironolactone on muscle sympathetic nerve activity in hypertensive patients. J Clin Endocrinol Metab 2009; 94:1361–6.

[21] Ames RP, Peacock PB. Serum cholesterol during treatment of hypertension with diuretic drugs. Arch Intern Med 1984;144:710–4.

[22] Yutaka M, Mifune M, Kubota E, et al. Comparison of effects of low dose of spironolactone and a thiazide diuretic in patients with hypertension treated with an angiotensin-converting enzyme inhibitor or an angiotensin type 1 receptor blocker. Clin Exp Hypertens 2009;31:648–56.

[23] Schrijver G, Weinberger MH. Hydrochlorothiazide and spironolactone in hypertension. Clin Pharmacol Ther 1979;25:33–42.
[24] Falch DK, Schreiner A. The effect of spironolactone on lipid, glucose and uric acid levels in blood during long-term administration to hypertensives. Acta Med Scand 1983;213:27–30.
[25] Jeunemaitre X, Charru A, Chatellier G, et al. Long-term metabolic effects of spironolactone and thiazides combined with potassium-sparing agents for treatment of essential hypertension. Am J Cardiol 1988;62:1072–7.
[26] Jeunemaitre X, Chatellier G, Kreft-Jais C, et al. Efficacy and tolerance of spironolactone in essential hypertension. Am J Cardiol 1987;60: 820–5.
[27] Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension 2007;49:839–45.
[28] McMurray EM, Wallace IR, Ennis C, et al. Effect of eplerenone on insulin action in essential hypertension: a randomised, controlled, crossover study. J Hum Hypertens 2014;28:575–8.
[29] Yano Y, Hoshide S, Tamaki N, et al. Efficacy of eplerenone added to renin-angiotensin blockade in elderly hypertensive patients: the Jichi-Eplerenone Treatment (JET) study. J Renin Angiotensin Aldosterone Syst 2011;12:340–7.
[30] Sato A, Fukuda S. Clinical effects of eplerenone, a selective aldosterone blocker, in Japanese patients with essential hypertension. J Hum Hypertens 2010;24:387–94.
[31] Garg R, Kneen L, Williams GH, et al. Effect of mineralocorticoid receptor antagonist on insulin resistance and endothelial function in obese subjects. Diabetes Obes Metab 2014;16:268–72.
[32] Lovejoy JC, Bray GA, Bourgeois MO, et al. Exogenous androgens influence body composition and regional body fat distribution in obese postmenopausal women—a clinical research center study. J Clin Endocrinol Metab 1996;81:2198–203.
[33] Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, et al. A randomized study of the beneficial effects of aldosterone antagonism on LV function, structure, and fibrosis markers in metabolic syndrome. JACC Cardiovasc Imaging 2011;4:1239–49.
[34] Costa MB, Andrade Ezequiel DG, Morais Lovis JC, et al. Aldosterone antagonist decreases blood pressure and improves metabolic parameters in obese patients with the metabolic syndrome. J Clin Hypertens 2010;12:753–5.
[35] Lovisi JC, Ezequiel DA, Costa MB, et al. Espironolactone improves flow-mediated vasodilatation in subjects with the metabolic syndrome. J Bras Nefrol 2011;33:463–6.
[36] Kanchan V, Pawan K, Sudhir V, et al. Effect of low-dose mineralocorticoid receptor antagonists on metabolic profile and endothelial dysfunction in metabolic syndrome. Diabetes Metab 2016;42:65–8.
[37] Hwang MH, Yoo JK, Luttrell M, et al. Effect of selective mineralocorticoid receptor blockade on flow-mediated dilation and insulin resistance in older adults with metabolic syndrome. Metab Syndr Relat Disord 2015;13:356–61.
[38] Derosa G, Bonaventura A, Bianchi L, et al. Effects of canrenone in patients with metabolic syndrome. Expert Opin Pharmacother 2013; 14:2161–9.
[39] Derosa G, Romano D, Bianchi L, et al. The effects of canrenone on inflammatory markers in patients with metabolic syndrome. Ann Med 2015;47:47–52.
[40] Swaminathan K, Davies J, George J, et al. Spironolactone for poorly controlled hypertension in type 2 diabetes: conflicting effects on blood pressure, endothelial function, glycaemic control and hormonal profiles. Diabetologia 2008;51:762–8.
[41] Davies JI, Band M, Morris A, et al. Spironolactone impairs endothelial function and heart rate variability in patients with type 2 diabetes. Diabetologia 2004;47:1687–94.
[42] Nielsen SE, Persson F, Frandsen E, et al. Spironolactone diminishes urinary albumin excretion in patients with type 1 diabetes and microalbuminuria: a randomized placebo-controlled crossover study. Diabet Med 2012;29:e184–90.
[43] Rossing K, Schjoedt KJ, Smidt UM, et al. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. Diabetes Care 2005;28:2106–12.
[44] Schjoedt KJ, Rossing K, Juhl TR, et al. Beneficial impact of spironolactone in diabetic nephropathy. Kidney Int 2005;68:2829–36.
[45] van den Meiracker AH, Baggen RG, Pauli S, et al. Spironolactone in type 2 diabetic nephropathy: Effects on proteinuria, blood pressure and renal function. J Hypertens 2006;24:2285–92.
[46] Oxlund CS, Henriksen JE, Tarnow L, et al. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. J Hypertens 2013;31:2094–102.
[47] Schjoedt KJ, Rossing K, Juhl TR, et al. Beneficial impact of spironolactone on nephrotic range albuminuria in diabetic nephropathy. Kidney Int 2006;70:536–42.
[48] Takebayashi K, Matsumoto S, Aso Y, et al. Aldosterone blockade attenuates urinary monocyte chemoattractant protein-1 and oxidative stress in patients with type 2 diabetes complicated by diabetic nephropathy. J Clin Endocrinol Metab 2006;91:2214–7.
[49] Matsumoto S, Takebayashi K, Aso Y. The effect of spironolactone on circulating adipocytokines in patients with type 2 diabetes mellitus complicated by diabetic nephropathy. Metabolism 2006;55:1645–52.
[50] Mehdi UF, Adams-Huet B, Raskin P, et al. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol 2009;20:2641–50.
[51] Garg R, Rao AD, Baimas-George M, et al. Mineralocorticoid receptor blockade improves coronary microvascular function in individuals with type 2 diabetes. Diabetes 2015;64:236–42.
[52] Momeni A, Behradmanesh MS, Kheiri S, et al. Evaluation of spironolactone plus hydrochlorothiazide in reducing proteinuria in type 2 diabetic nephropathy. J Renin Angiotensin Aldosterone Syst 2015;16:113–8.
[53] Viswanathan V, Mohan V, Subramani P, et al. Effect of spironolactone and amiloride on thiazolidinedione-induced fluid retention in South Indian patients with type 2 diabetes. Clin J Am Soc Nephrol 2013;8:225–32.
[54] Karalliedde J, Buckingham R, Starkie M, et al. Effect of various diuretic treatments on rosiglitazone-induced fluid retention. J Am Soc Nephrol 2006;17:3482–90.
[55] Davidson MB, Wong A, Hamrahian AH, et al. Effect of spironolactone therapy on albuminuria in patients with type 2 diabetes treated with angiotensin-converting enzyme inhibitors. Endocr Pract 2008;14:985–92.
[56] Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol 2006;1:940–51.
[57] Joffe HV, Kwong RY, Gerhard-Herman MD, et al. Beneficial effects of eplerenone versus hydrochlorothiazide on coronary circulatory function in patients with diabetes mellitus. J Clin Endocrinol Metab 2007;92:2552–8.
[58] Karashima S, Yoneda T, Kometani M, et al. Angiotensin II receptor blocker combined with eplerenone or hydrochlorothiazide for hypertensive patients with diabetes mellitus. Clin Exp Hypertens 2016;38:565–70.
[59] Fogari R, Derosa G, Zoppi A, et al. Comparative effect of canrenone or hydrochlorothiazide addition to valsartan/amlodipine combination on urinary albumin excretion in well-controlled type 2 diabetic hypertensive patients with microalbuminuria. Expert Opin Pharmacother 2014;15:453–9.
[60] Ogino K, Kinugasa Y, Kato M, et al. Spironolactone, not furosemide, improved insulin resistance in patients with chronic heart failure. Int J Cardiol 2014;171:398–403.
[61] Preiss D, Zetterstrand S, McMurray JJ, et al. Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. Diabetes Care 2009;32:915–20.
[62] Preiss D, van Veldhuisen DJ, Sattar N, et al. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail 2012;14:909–15.
[63] Ukena C, Dobre D, Mahfoud F, et al. Hypo- and hyperglycemia predict outcome in patients with left ventricular dysfunction after acute myocardial infarction: data from EPHESUS. J Card Fail 2012;18:439–45.
[64] Yamaji M, Tsutamoto T, Kawahara C, et al. Effect of eplerenone versus spironolactone on cortisol and hemoglobin A(1)(c) levels in patients with chronic heart failure. Am Heart J 2010;160:915–21.
[65] Ganie MA, Khurana ML, Nisar S, et al. Improved efficacy of low-dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six-month, open-label randomized study. J Clin Endocrinol Metab 2013;98:3599–607.
[66] Vieira CS, Martins WP, Fernandes JB, et al. The effects of 2 mg chlormadinone acetate/30 mcg ethinylestradiol, alone or combined with spironolactone, on cardiovascular risk markers in women with polycystic ovary syndrome. Contraception 2012;86:268–75.

[67] Mazza A, Fruci B, Guzzi P, et al. In PCOS patients the addition of low-dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism than metformin alone. Nutr Metab Cardiovasc Dis 2014;24:132–9.
[68] Kebapcilar L, Taner CE, Kebapcilar AG, et al. Comparison of four different treatment regimens on coagulation parameters, hormonal and metabolic changes in women with polycystic ovary syndrome. Arch Gynecol Obstet 2010;281:35–42.
[69] Diri H, Karaburgu S, Acmaz B, et al. Comparison of spironolactone and spironolactone plus metformin in the treatment of polycystic ovary syndrome. Gynecol Endocrinol 2016;32:42–5.
[70] Kebapcilar L, Bilgir O, Taner CE, et al. Oral contraceptives alone and with spironolactone increase sCD40 ligand in PCOS patients. Arch Gynecol Obstet 2010;281:539–43.
[71] Meyer C, McGrath BP, Teede HJ. Effects of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome. Diabetes Care 2007;30:471–8.
[72] Studen KB, Sebestjen M, Pfeifer M, et al. Influence of spironolactone treatment on endothelial function in non-obese women with polycystic ovary syndrome. Eur J Endocrinol 2011;164:389–95.
[73] Nakhjavani M, Hamidi S, Esteghamati A, et al. Short term effects of spironolactone on blood lipid profile: a 3-month study on a cohort of young women with hirsutism. Br J Clin Pharmacol 2009;68:634–7.
[74] Shoupe D, Lobo RA. The influence of androgens on insulin resistance. Fertil Steril 1984;41:385–8.
[75] Zulian E, Sartorato P, Benedini S, et al. Spironolactone in the treatment of polycystic ovary syndrome: effects on clinical features, insulin sensitivity and lipid profile. J Endocrinol Invest 2005;28:49–53.
[76] Moghetti P, Tosi F, Castello R, et al. The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women. J Clin Endocrinol Metab 1996;81:952–60.
[77] Wild RA, Demers LM, Applebaum-Bowden D, et al. Hirsutism: metabolic effects of two commonly used oral contraceptives and spironolactone. Contraception 1991;44:113–24.
[78] Kulshreshtha B, Gupta N, Ganie MA, et al. Effect of metformin and spironolactone therapy on OGTT in patients with polycystic ovarian syndrome—a retrospective analysis. Gynecol Endocrinol 2012;28: 823–6.
[79] Sindelka G, Widimsky J, Haas T, et al. Insulin action in primary hyperaldosteronism before and after surgical or pharmacological treatment. Exp Clin Endocrinol Diabetes 2000;108:21–5.
[80] Strauch B, Widimsky J, Sindelka G, et al. Does the treatment of primary hyperaldosteronism influence glucose tolerance? Physiol Res 2003;52:503–6.
[81] Catena C, Lapenna R, Baroselli S, et al. Insulin sensitivity in patients with primary aldosteronism: a follow-up study. J Clin Endocrinol Metab 2006;91:3457–63.
[82] Mosso LM, Carvajal CA, Maiz A, et al. A possible association between primary aldosteronism and a lower beta-cell function. J Hypertens 2007;25:2125–30.
[83] Hosoya K, Minakuchi H, Wakino S, et al. Insulin resistance in chronic kidney disease is ameliorated by spironolactone in rats and humans. Kidney Int 2015;87:749–60.
[84] Michea L, Vukusich A, Gonzalez M, et al. Effect of spironolactone on K(+) homeostasis and ENaC expression in lymphocytes from chronic hemodialysis patients. Kidney Int 2004;66:1647–53.
[85] Arase Y, Suzuki F, Suzuki Y, et al. Losartan reduces the onset of type 2 diabetes in hypertensive Japanese patients with chronic hepatitis C. J Med Virol 2009;81:1584–90.
[86] Polyzos SA, Kountouras J, Zafeiriadou E, et al. Effect of spironolactone and vitamin E on serum metabolic parameters and insulin resistance in patients with nonalcoholic fatty liver disease. J Renin Angiotensin Aldosterone Syst 2011;12:498–503.
[87] Dhillon S. Eplerenone: a review of its use in patients with chronic systolic heart failure and mild symptoms. Drugs 2013;73:1451–62.
[88] van Deursen VM, Damman K, van der Meer P, et al. Co-morbidities in heart failure. Heart Fail Rev 2014;19:163–72.
[89] Zhang Y, Hu G, Yuan Z, et al. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with type 2 diabetes: a systematic review and meta-analysis. PloS One 2012;7:e42551.
[90] Gerstein HC, Swedberg K, Carlsson J, et al. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Arch Intern Med 2008;168:1699–704.
[91] IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol 2014;14:25.
[92] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[93] Armanini D, Sabbadin C, Dona G, et al. Aldosterone receptor blockers spironolactone and canrenone: two multivalent drugs. Expert Opin Pharmacother 2014;15:909–12.
[94] Gillespie EL, White CM, Kardas M, et al. The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. Diabetes Care 2005;28:2261–6.
[95] Zhao JV, Xu L, Lin SL, et al. Spironolactone and glucose metabolism, a systematic review and meta-analysis of randomized controlled trials. J Am Soc Hypertens 2016;10:671–82.
[96] Sowers JR, Whaley-Connell A, Epstein M. Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. Ann Intern Med 2009;150:776–83.
[97] Hammer F, Stewart PM. Cortisol metabolism in hypertension. Best practice & research. Clin Endocrinol Metab 2006;20:337–53.
[98] Young EA, Lopez JF, Murphy-Weinberg V, et al. The role of mineralocorticoid receptors in hypothalamic-pituitary-adrenal axis regulation in humans. J Clin Endocrinol Metab 1998;83:3339–45.
[99] Anagnostis P, Athyros VG, Tziomalos K, et al. Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. J Clin Endocrinol Metab 2009;94:2692–701.
[100] Chiodini I, Adda G, Scillitani A, et al. Cortisol secretion in patients with type 2 diabetes: relationship with chronic complications. Diabetes Care 2007;30:83–8.
[101] Varughese AG, Nimkevych O, Uwaifo GI. Hypercortisolism in obesity-associated hypertension. Curr Hypertens Rep 2014;16:443.
[102] Yamaji M, Tsutamoto T, Kawahara C, et al. Serum cortisol as a useful predictor of cardiac events in patients with chronic heart failure: the impact of oxidative stress. Circ Heart Fail 2009;2:608–15.
[103] Krarup T, Krarup T, Hagen C. Do patients with type 2 diabetes mellitus have an increased prevalence of Cushing's syndrome? Diabetes Metab Res Rev 2012;28:219–27.
[104] Jankowska EA, Filippatos G, Ponikowska B, et al. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. J Card Fail 2009;15:442–50.
[105] Jankowska EA, Drohomirecka A, Ponikowska B, et al. Deficiencies in circulating testosterone and dehydroepiandrosterone sulphate, and depression in men with systolic chronic heart failure. Eur J Heart Fail 2010;12:966–73.
[106] Al Hayek AA, Khader YS, Jafal S, et al. Prevalence of low testosterone levels in men with type 2 diabetes mellitus: a cross-sectional study. J Family Community Med 2013;20:179–86.
[107] Grossmann M. Testosterone and glucose metabolism in men: current concepts and controversies. J Endocrinol 2014;220:R37–55.