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 (HbA1c) 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 HbA1c in diabetic patients, spironolactone had a nonsignificant effect in parallel-group studies (mean difference 0.03 [−0.20;0.26]), but significantly increased HbA1c 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, HbA1c = glycated hemoglobin, HCTZ = hydrochlorothiazide, HF = heart failure, HOMA-IR = homeostatic model assessment of β-cell function, HOMA-βFI = homeostatic 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
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 (EPI), 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, and in reducing the risk of morbidity and mortality in HF patients. \[3\] MRAs are also used for the treatment of primary aldosteronism \[5\] and edema associated with liver cirrhosis or nephrotic syndrome. \[6\]

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, \[7\] inhibition of estrogen sulfatase and 17β-HSD type 1 which leads to increases in estradiol pool. \[8\] These mechanisms cause gynecomastia, breast tenderness, menstrual irregularities \[9\] and erectile dysfunction. \[10\] Although these off-target effects are undesirable in most conditions, they are useful for the treatment of disorders related to hyperandrogenism. \[11\] Thus, SPIRO is also a treatment for idiopathic hirsutism \[12\] and polycystic ovary syndrome (PCOS), a disease characterized by excess androgens, oligoovulation or anovulation and/or polycystic ovaries. \[13\]

There is a growing amount of evidence suggesting that SPIRO’s “off-target” effects could also include detrimental effects on glucose homeostasis. \[14\] 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. \[15\] 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 \[16\] 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 \[17\]. 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 glyced hemoglobin (HbA1c) 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 HbA1c and that had a comparator group were also included into quantitative
analyses. As HbA1c 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. HbA1c 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). 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.

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. 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 HbA1c. 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

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**Figure 1. Flow of information.**

- Records identified Medline searching (n = 1682)
- Additional records identified through other sources (n = 12)
- Records removed due to language barrier (n = 117); reviews, case reports and commentaries removed (n = 338)
- Records screened (n = 1239)
- Additional records identified through other sources (n = 12)
- Full-text articles excluded (n = 35)
  - Use of a combination of a thiazide diuretic with spironolactone, with no comparator group (n = 2)
  - Use of a combination of oral contraceptives with SPIRO, with no comparator group (n = 1)
  - Treatment did not include MRAs (only use of adenectomy n = 1; only use of other renin-angiotensin-aldosterone blockers n = 1)
  - Treatment period < 7 days (n = 2)
  - Only aggregate results of surgery and MRA provided for the treatment of hyperaldosteronism (n = 3)
  - Effect of MRA on glucose homeostasis not analyzed (n = 23)
  - No information provided on the exact MRA or the other set of medications used in combination therapy (n = 1)
  - Article retracted (n = 1)
- Studies included in qualitative synthesis (n = 72)
- Studies included in quantitative synthesis – meta-analysis (n = 12)
- Records excluded (n = 1132: 873 title, 259 abstract)
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 HbA1c, 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 HbA1c.[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.[19] 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.[16] 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. HbA1c 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 1

| 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) | SPIRO did not affect progressive increase in cortisol and 17OHCExcretion during ACTH or cortisol administration, SPIRO did not affect the increase in glucose caused by administration of 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 | RU486: significantly lower glucose concentration, failure of insulin to increase during cortisol administration compared with control value |
| Knug 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 |

17OHC = 17 hydroxycorticosteroid, ACTH = adrenocorticotropic hormone, EPLE = eplerenone, HOMA-IR = homeostasis model assessment of insulin resistance, SPIRO = spironolactone.
| Author         | Year | Study design                                      | Patients disease                      | Follow-up | Medication dose                                  | Results of markers                                                                 |
|---------------|------|--------------------------------------------------|---------------------------------------|-----------|-------------------------------------------------|------------------------------------------------------------------------------------|
| Scherstén B   | 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     | 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      | 2012 | Randomized, single-blind, crossover design       | 17 patients with hypertension         | 12 wk     | Chlorthalidone 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      | 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, F = 2.3, p = .011 difference between baseline and 2 treatment phases) No effect on insulin, QUICKI or HOMA-IR, contrary to chlorthalidone |
| Ames RP       | 1984 | Randomized, unblinded study                      | 23 patients with hypertension         | 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      | 2009 | Prospective, randomized trial                    | 64 patients with hypertension         | 6 mo      | SPIRO 25 mg versus HCTZ 2 mg 3 dwk (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 HbA1c with SPIRO (5.4 ± 0.4 to 5.3 ± 0.4%, P = .0471) |
| Schrijver G   | 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: significant rise in blood glucose only with SPIRO 400 mg/d (P < .05); Double-drug treatment: significant decrease in glucose levels with SPIRO 100 mg/d plus placebo (P < .05) and significant increase in glucose levels |

(continued)
| Author | Year | Study design | Patients disease | Follow-up | Medication dose | Results of markers |
|--------|------|--------------|------------------|-----------|----------------|--------------------|
| Falch DK | 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. HbA1c unchanged from 6 to 12 mo (not measured at baseline). |
| Jeunemaitre X | 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 | 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 NP | 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 (2.73)-mean difference 0.19 (P = .009) |
| McMurray EM | 2014 | Randomized, controlled, double-blind, crossover trial | 15 patients with essential hypertension | 12 wk each treatment (6 wk washout from antihypertensive medication, 6 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 = .083). |
| Yano Y | 2011 | Prospective, no control group | 20 elderly patients with essential hypertension | 24 wk | | No significant change in fasting glucose (P = .848) and insulin (P = .468). |
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 HbA1c. 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 HbA1c.

Sixteen studies evaluated SPIRO. Among the 15 studies that measured HbA1c, 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, HbA1c (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. HbA1c 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.[79]

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 HbA1c, or the incidence of diabetes. Rather, the

| Table 2 (continued) |
|----------------------|
| Author               |
| Year                 |
| Study design         |
| Medication dose       |
| Follow-up            |
| Patients disease      |
| Results of markers    |
|                      |
| Sato A[30]           |
| 2010                 |
| Prospective, open-label, no control group |
| EPLE 25 mg (10 patients), 50 mg/d (10 patients), mean 37.5 ± 12.8 mg/d (added to ACE inhibitor/ARB) |
| 24 wk                |
| 68 patients with essential hypertension |
| No change in HbA1c   |

AUC = area under curve, EPLE = eplerenone, HbA1c = glycated hemoglobin, HCTZ = hydrochlorothiazide, HOMA-IR = homeostasis model assessment of insulin resistance, QUICKI = quantitative insulin sensitivity check index, SPIRO = spironolactone, TCTZ = trichlormethiazide.
Table 3

| 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/m²)                 | 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 group. |
| Lovel J[32] | 2014 | Placebo-controlled, double-blind, randomized, parallel-group study | 30 healthy obese postmenopausal women, 15 in each group (3 dropped-out, 1 from SPIRO group) | 9 mo      | SPIRO 25 mg/d versus nandrolone decaionate 30 mg/wk (weak androgen) versus placebo, added to low-fat weight reducing diet | No significant treatment effects on fasting glucose, insulin, insulin sensitivity index (S), glucose effectiveness (S_e), and glucose tolerance (K_g). |
| Kosmula 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 glucose metabolism (but in table significant decrease in glucose in SPIRO phase, and slight decrease in 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 fasting insulin, fasting glucose or HOMA-IR. |
| Lovel JOM[35] | 2011 | Prospective, no control group       | 19 patients with metabolic syndrome                  | 16 wk     | SPIRO 50 mg/d                 | No significant 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). No significant effect on fasting plasma glucose, fasting plasma insulin, or HOMA-IR. |
| 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 change in insulin resistance (HOMA-IR 1.04±0.26 vs 1.36±0.50, P=.6). Alternate hypothesis was that it would exert a beneficial effect (no precision whether test was 1 sided). |
| 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 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 (9.91±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/mg) compared with baseline (P<.05) and placebo (P<.05). |
| 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 (117±7.4 to 96.2±5.0 mg/dL, P<.05 versus baseline, P<.05 versus placebo. No decrease in placebo. |
| 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 a day till end of study (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 (117±7.4 to 96.2±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.
| Author          | Year | Study design                      | Patients disease                                                                 | Follow-up | Medication dose | Results of markers                     |
|-----------------|------|-----------------------------------|-----------------------------------------------------------------------------------|-----------|-----------------|----------------------------------------|
| Swaminathan     | 2008 | Randomized, placebo-controlled,   | 50 patients with diabetes and hypertension (38 completed the study)               | 10 wk     | 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 HbA1c compared to placebo (P = 0.01), mean difference in cortisol of 92.4 nmol/L compared to placebo (P = 0.003) |
| Davies J        | 2004 | Prospective, randomized, double-blind trial (crossover) | 42 patients with diabetes, without HF (baseline characteristics compared with healthy volunteers) | 10 wk     | SPIRO 50 mg/d or placebo for 1 mo, then 2 wk washout, then 1 mo crossover | Significant increase in HbA1c of 0.24 ± 0.08% (P = 0.003) and cortisol (508.9 [157.4] nmol/L vs placebo 455.8 [151.3] nmol/L; P < 0.05) |
| Nielsen SE      | 2012 | Double-blind, randomized, placebo-controlled crossover study | 21 patients with type I diabetes and microalbuminuria (20 patients completed) | 4 mo      | SPIRO 25 mg/d or placebo | Significant increase in HbA1c from 8.2 ± 0.2 to 8.6 ± 0.3% (mean difference of 0.4; P = 0.03) in HbA1c |
| Rossing K       | 2005 | Randomized, double-blind, crossover study | 21 patients with type II diabetes and nephropathy (20 patients completed) | 16 wk     | SPIRO 25 mg/d for 8 wk or placebo for 8 wk | Slight but statistically significant increase from 7.8 ± 0.4 to 8.1 ± 0.3% (mean difference of 0.3; P = 0.03) in HbA1c |
| Schoedt KJ      | 2005 | Double-blind, randomized, crossover trial | 20 patients with diabetes and macroalbuminuria | 4 mo      | SPIRO 25 mg/d or placebo | Nonsignificant increase in HbA1c from 8.4 (0.2) to 8.6 (0.2)% (mean difference 0.2 (−0.01 to 0.4) |
| van den Meiracker AH | 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 HbA1c of 0.03 (−0.34 to 0.42%) with SPIRO, versus placebo 0.14 (−0.22 to 0.05%) (P value not given) |
| Oetlund CS      | 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, HbA1c analyzed for 61 patients) or placebo (55 patients completed, HbA1c analyzed for 58 patients) added to previous triple antihypertensive treatment Un titration to 50 mg if blood pressure not lowered | No change in HbA1c (P = 0.23) |
| Schoedt KJ      | 2006 | Randomized, double-blind, placebo-controlled, crossover trial | 20 patients with type I or type II diabetes, diabetic nephropathy, hypertension (53 remained) | 4 mo      | SPIRO 25 mg/d or placebo | No change in HbA1c (P = 0.20) |
| Takebayashi K   | 2006 | Randomized, parallel-group         | 37 patients with type II diabetes and diabetic nephropathy (25 matched controls) | 3 mo      | SPIRO 50 mg (23 patients) or amlodipine (14 patients) | Significant increase in HbA1c, from 7.6 ± 1.4 to 8.2 ± 1.4% (P = 0.0059) with SPIRO, versus nonsignificant increase in comparator amlodipine 7.7 ± 1.8 to 7.5 ± 1.4% (P = 0.702) Difference between 2 groups P = 0.0624 No change in fasting plasma glucose (P = 0.8569) Significant increase in HbA1c, from 7.6 ± 1.4 to 8.2 ± 1.5% (P = 0.0025) and adiponectin only with SPIRO |
| Matsumoto S     | 2006 | Prospective, randomized           | 33 patients with diabetes, nephropathy, without clinically apparent symptoms of chronic HF | 3 mo      | SPIRO 50 mg or amlodipine | (continued) |
| Author          | Year   | Study design                     | Patients disease                                                                 | Follow-up | Medication dose                                                                 | Results of markers                                                                 |
|-----------------|--------|----------------------------------|----------------------------------------------------------------------------------|-----------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 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 HbA₁c. Glucose levels fluctuated similarly in the groups. Fasting glucose was lower at baseline in SPIRO group compared to HCTZ. No significant change between groups SPIRO vs HCTZ: glucose P = 0.91, HbA₁c P = 0.94; SPIRO vs HCTZ + placebo glucose P = 0.52, HbA₁c P = 0.64 |
| Gang 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 = 0.91, HbA₁c P = 0.94; SPIRO vs HCTZ + placebo glucose P = 0.52, HbA₁c P = 0.64 |
| 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 HCTZ 50 mg/d plus HCTZ 25 mg/d plus placebo   | No significant changes between groups SPIRO vs HCTZ + placebo glucose P = 0.52, HbA₁c P = 0.64 |
| 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 | SPIRO: no significant differences in HbA₁c, glucose 10.5 ± 3.9 mg/dL. HCTZ: no significant differences in HbA₁c, glucose 10.5 ± 3.9 mg/dL. |
| Karaliidde 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 | No significant changes in glycemic control in any of the groups (HbA₁c, glucose, fructosamine) |
| 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 | SPIRO: no significant changes in HbA₁c, 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 HbA₁c, glucose, fructosamine |
| Joffe HV[57]    | 2007   | Randomized, double-blind crossover study | 16 patients with diabetes, albuminuria, no clinical cardiovascular disease     | 16 wk (8 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) | SPIRO: no significant changes in HbA₁c, glucose, fructosamine |

(continued)
### Table 4 (continued)

| Author          | Year   | Study design            | Patients disease | Medication dose | Follow-up | Results of markers                                                                                                                                 |
|-----------------|--------|-------------------------|------------------|----------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Karashima S     | 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 hypertension and microalbuminuria | EPLE 50 mg/d (added to candesartan 8 mg) | 12 mo     | No significant effect on HbA1c (12.5 ± 0.3 to 13.2 ± 0.4 mmol/L, P < .05) and no significant increase in aldosterone. No significant difference between groups in either group. |
| Fogari R        | 2014   | Prospective, randomized, probably double-blind, parallel group study | 120 patients with type II diabetes, hypertension and microalbuminuria | Canrenone 25 mg versus HCTZ | 6 mo      | No changes in fasting plasma glucose or HbA1c. HCTZ: significant increase in HbA1c (6.36 ± 0.18% to 6.50 ± 0.20%). No significant difference between groups. |

**Table 8**

| Study design          | Patients disease                                                                 | Medication dose                                                                 | Follow-up | Results of markers                                                                                                                                 |
|-----------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 hypertension and microalbuminuria | EPLE 50 mg/d (added to candesartan 8 mg) | 12 mo    | No significant effect on HbA1c (12.5 ± 0.3 to 13.2 ± 0.4 mmol/L, P < .05) and no significant increase in aldosterone. No significant difference between groups in either group. |

3.1.7. **Hyperaldosteronism.** Four articles were published on the effect of SPIRO in primary hyperaldosteronism (Table 7). Three of these studies were prospective, without randomization. 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. 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. HbA1c was used as a biomarker in only 1 study, 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 and 1 sequential fixed-dose study. One retrospective cohort study evaluated patients with hypertension and hepatitis C. A fourth article presented preliminary results of an RCT on patients with nonalcoholic fatty liver disease. Sample sizes varied widely between 9 and 240 patients, and the duration of follow-up also differed from 3 weeks to 3.4 years. SPIRO was administered at doses of 25 to 50 mg. HbA1c 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 HbA1c. 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 HbA1c between SPIRO and the comparator group was nonsignificant (mean difference 0.03 [95% CI: –0.20 to 0.26]).
| Author          | Year  | Study design                          | Patients disease          | Follow-up                  | Medication dose          | Results of markers                                                                 |
|-----------------|-------|---------------------------------------|---------------------------|----------------------------|----------------------------|-------------------------------------------------------------------------------------|
| Ogino K[^60^]   | 2014  | Double-blind, randomized,             | 16 patients with chronic  | 32 wk (16-wk treatment    | SPIRO 25 mg/d versus      | No change in fasting plasma glucose                                                |
|                 |       | controlled, crossover study           | HF                        | periods with 4-wk washout  | furosemide 20 mg/d        | Improvement in fasting insulin (5.3 ± 0.5 to 2.8 ± 0.4 μU/mL, *P* = .001) and HOMA-IR (1.42 ± .17 to 0.71 ± .10, *P* = .004) with SPIRO, but not with furosemide (difference between groups: *P* = .0001 for insulin and *P* = .0003 for HOMA-IR) |
| Preiss D[^61^]  | 2009  | Retrospective cohort study:           | 1620 nondiabetic patients | 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) |
|                 |       | substudy of CHARM                     | with chronic HF           |                            |                            |                                                                                     |
| Preiss D[^62^]  | 2012  | Substudy of EMPHASIS                  | 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                                             |
|                 |       | (randomized, double-blind, placebocontrolled trial) |                           |                            |                            |                                                                                     |
| Ukena C[^63^]   | 2012  | Substudy of EPHE/SUS study            | 6497 patients with acute myocardial infarction, LVEF <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 |
|                 |       | (multicenter, randomized, double blind trial) |                           |                            |                            |                                                                                     |
| Yamaji M[^64^]  | 2010  | Prospective, open-label,              | 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 HbA1c, 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), HbA1c (*P* = .0003), and adiponectin (*P* = .03) Significant positive correlation between change in cortisol and change in HbA1c, with SPIRO (*P* = .003) |
|                 |       | randomized                             | Blinding not mentioned     |                            |                            |                                                                                     |

EPLE = eplerenone, HF = heart failure, HOMA-IR = homeostasis model assessment of insulin resistance, SPIRO = spironolactone.
| 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 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 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 \( P < .001)\) |
| 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 30 controls          | 6 mo (21 d treatment, 7 d pause) | 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) | 3 mo        | SPIRO average 100 mg/d                                                          | No significant change in glucose |
| Shoupe D[74]    | 1984 | Prospective, no control group     | 14 patients with idiopathic hirsutism (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 IR or T PCOS: significantly lowered T and IR IR: 20.0±2.2 to 11.2±2.0 with SPIRO in PCOS \( P < .05 \) compared with baseline |

(continued)
| Author         | Year | Study design                                      | Patients disease | Follow-up | Medication dose | Results of markers                                                                 |
|---------------|------|--------------------------------------------------|------------------|-----------|----------------|-----------------------------------------------------------------------------------|
| Zulian E[75]  | 2005 | Prospective clinical trial, no control group     | 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     | 43 women with PCOS | 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 Increase in fasting insulin with SPIRO (P < .05) in Figure 2 No effect with comparator |
| Wild RA[77]   | 1991 | Prospective, assigned to treatment based on      | 51 women with PCOS | 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 = .039) Post-OGTT: Significant reduction in 2-h insulin: 85.9 ± 10.4 to 69.0 ± 81.7 (P = .02) Metformin: Pre-OGTT: Significant decrease in insulin: 17.7 ± 16.8 to 11.0 ± 6.3 (P = .04) 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 insulin (135.9 ± 74.9 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 ± 73.3, P = .01) |

AGT = abnormal glucose tolerance, AUC = area under curve, HOMA-IR = homeostasis model assessment of insulin resistance, IH = idiopathic hirsutism, IR = fasting immunoreactive insulin, NGT = normal glucose tolerance, OC = oral contraceptive, OGTT = oral glucose tolerance test, PCOS = polycystic ovary syndrome, SPIRO = spironolactone, T = testosterone.
| Author          | Year | Study design       | Patients disease                                                                 | Follow-up | Medication dose                                                                 | Results of markers                                                                 |
|-----------------|------|--------------------|----------------------------------------------------------------------------------|-----------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Sindelka G     | 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 | Slight increase in HbA1c ($P < .05$) Worsening in insulin action (glucose disposal rate, insulin sensitivity index, metabolic clearance rate of glucose) Adrenalectomy: improvement in insulin action |
| Strauch B      | 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 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) |
| Catena C       | 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) | Increase in insulin from 6.88 ± 5.33 to 13.39 ± 6.66 ($P = .048$) and C-peptide from 0.62 ± 0.57 to 3.32 ± 1.24 ($P < .001$) no changes in glucose, HOMA-IR or HOMA-$\beta$F |
| Mosso LM       | 2007 | Non intervention, 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 6.88 ± 5.33 to 13.39 ± 6.66 ($P = .048$) and C-peptide from 0.62 ± 0.57 to 3.32 ± 1.24 ($P < .001$) no changes in glucose, HOMA-R or HOMA-$\beta$F |

APA = aldosterone producing adenoma, AUC = area under curve, BMI = body mass index, EH = essential hypertension, HbA1c = glycated hemoglobin, HOMA-$\beta$F = homeostatic model assessment of $\beta$-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.
| Author        | Year | Study design                                | Patients disease                                      | Follow-up | Medication dose                      | Results of markers                                                                                                                                 |
|--------------|------|---------------------------------------------|------------------------------------------------------|-----------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Hosoya K     | 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 $29.0 \pm 13.1$ versus SPIRO $53.7 \pm 6.5; P < .01$ $%$ change fasting insulin control $25.7 \pm 11.7$ versus SPIRO $51.2 \pm 7.1; P < .01$ |
| Michea L     | 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                                                                                 | No significant difference between the 3 phases in plasma glucose or insulin, before and after potassium-carbohydrate load |
| Arase Y      | 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 ($P = .029$)                                                                 |
| Polyzos SA  | 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 $\text{Favorable effect on insulin } 15.3 \pm 2.7 \text{ to } 10.3 \pm 1.6 (P < .05)$ and HOMA-IR $4.4 \pm 0.9 \text{ to } 2.8 \pm 0.5 (P < .05)$ $\text{Non significant increase in QUICKI}$ 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 melitus.
| 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 (HbA1c 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, HbA1c (only in 3 studies)  
| Results:  
|                         | - Spironolactone: heterogeneous  
|                         | - More positive on glycemia versus chlorothalidone  
|                         | - 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: HbA1c (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 HbA1c  
|                         | - 6 crossover studies: significantly negative effect on HbA1c (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, HbA1c (1 study)  
| Results: (continued) |
Table 9  
(continued).

| Health condition | Results |
|------------------|---------|
| **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 (HbA1c 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, HbA1c (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, HbA1c = 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.

**Parallel Studies**

| Study | Total | Mean | SD | Total | Mean | SD | MD | 95%-CI | Comparator | Tx Duration |
|-------|-------|------|----|-------|------|----|-----|-------|-----------|------------|
| Takebayashi, 2006 | 23 | 0.60 | 1.40 | 14 | -0.20 | 1.64 | -0.80 [-0.23; 1.83] | Amlodipine | 3 months |
| van den Meiracker, 2006 | 24 | 0.03 | 0.95 | 28 | 0.14 | 0.36 | -0.11 [-0.51; 0.29] | Placebo | 1 year |
| Oxlund, 2013 | 61 | 0.15 | 0.54 | 58 | 0.10 | 3.50 | 0.05 [-0.86; 0.96] | Placebo | 16 weeks |
| Viswanathan, 2013 | 60 | -0.94 | 2.63 | 60 | -0.99 | 3.89 | 0.05 [-1.14; 1.24] | Placebo+rosiglitazone* | 24 weeks |
| Gang, 2015 | 23 | 0.16 | 0.39 | 17 | 0.06 | 0.45 | 0.10 [-0.17; 0.37] | Placebo | 6 months |
| Momeni, 2015 | 20 | -0.26 | 1.07 | 20 | 0.06 | 1.03 | -0.32 [-0.97; 0.33] | Placebo+HCTZ** | 3 months |
| **Random effects model** | **211** | **197** | **0.03 [-0.20; 0.26]** |

*Study drug: SPIRO+rosiglitazone  
**Study drug: SPIRO+placebo

Figure 2. Meta-analysis of parallel-group 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 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 those on patients with hypertension, were inconclusive. These observations may also be related to the fact that HbA1c, 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 HbA1c, the average increase was, mostly, between 0.2% and 0.3%. The long-term effects of such increases in HbA1c remain largely unknown. However, such increases may have significant long-term clinical consequences as a 1% increase in HbA1c translates into a 15% increase in all-cause mortality and 25% increase in CV mortality in patients with diabetes.\(^{[18,20]}\)

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.\(^{[19]}\). From 18 RCTs, 8 studies provided information on the change in HbA1c. 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.\(^{[18,52]}\)) as well as 2 studies that could have potentially been included into their
metanalysis. In the meta-analysis of these studies, SPIRO was associated with a significant increase in Hba1c levels (mean difference 0.16; 95% CI 0.02–0.30). SPIRO’s impact on glucose, insulin, and HOMA-IR was nonsignificant. The value of Hba1c was slightly lower but in a similar range to the numeric value that we found in our crossover study (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 Hba1c 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 Hba1c 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 Hba1c, 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 Hba1c and the increase in cortisol, this glucocorticoid has been central to many hypotheses. SPIRO’s off-target effect on glucocorticoid receptors could lead to a reflex increase in cortisol, 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. 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). 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. 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 or an inhibition of the negative feedback on the hypothalamo-pituitary axis. Another hypothesis is that the increase in Hba1c may be due to a compensatory increase in aldosterone, as the non-genomic mineralocorticoid receptors are not blocked. 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, diabetes, hypertension, and HF. This hypothesis is supported by a high rate of diabetes in the Cushing syndrome, a disease characterized by cortisol excess.

The off-target anti-androgen effect of SPIRO may also play a role in modulating glycemia, because testosterone levels affect glucose homeostasis. SPIRO’s anti-androgenic effect may be either harmful or beneficial to glucose regulation, depending on the disease. In conditions that are characterized by hyper-androgenism, 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.

On the contrary, circulating levels of testosterone are decreased in disorders related to CV disease, such as HF and diabetes. It has been suggested that low levels of testosterone could also be associated with insulin resistance; 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. 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 (HbA1c, 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 HbA1c, 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. 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.

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