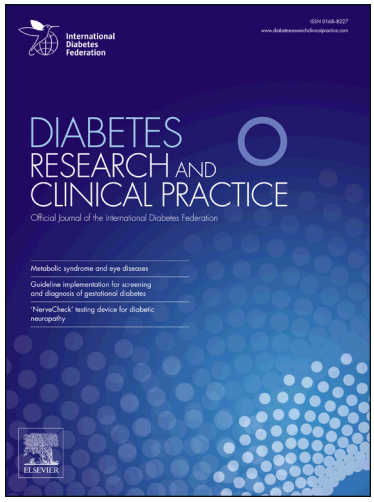

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Effects of reducing blood pressure on cardiovascular outcomes and mortality in patients with type 2 diabetes : focus on SGLT2 inhibitors and EMPA-REG OUTCOME

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Summary

Empagliflozin, a sodium-glucose cotransporter type 2 (SGLT2) inhibitor, has shown a remarkable reduction in cardiovascular and all-cause mortality in patients with type 2 diabetes (T2D) and antecedents of cardiovascular disease in the EMPA-REG OUTCOME trial. This effect has been attributed to a hemodynamic rather than a metabolic effect, partly due to the osmotic/diuretic effect of empagliflozin and to the reduction in arterial blood pressure. The present review will : 1) summarize the results of specific studies having tested the blood pressure lowering effects of SGLT2 inhibitors; 2) describe the results of meta-analyses of trials having evaluated the effects on mortality and cardiovascular outcomes of lowering blood pressure in patients with T2D, with a special focus on baseline and target blood pressures; 3) compare the cardiovascular outcome results in EMPA-REG OUTCOME versus other major trials with antihypertensive agents in patients with T2D; and 4) evaluate post-hoc analyses from EMPA-REG OUTCOME, especially subgroups of patients of special interest regarding the blood pressure lowering hypothesis. Although BP reduction associated to empagliflozin therapy may partly contribute to the benefits reported in EMPA-REG OUTCOME, other mechanisms most probably play a greater role in the overall CV protection and reduction in mortality observed in this trial.

Key words : Blood pressure – Diuretic - Empagliflozin - Heart failure - Hypertension – SGLT2 inhibitor - Type 2 diabetes

Introduction

Arterial hypertension is frequently associated with type 2 diabetes (T2D). These two bad companions markedly increase the risk of cardiovascular (CV) disease and premature death [1], and each of them, T2D [2] and hypertension [3], are well known independent CV risk factors. In the landmark United Kingdom Prospective Diabetes Study (UKPDS), reducing blood pressure (BP) in patients with newly diagnosed T2D and rather high BP resulted in a remarkable diminution in the incidence of diabetes-related complications, among which CV events and CV mortality [4]. These favourable results, in fact better than those obtained with intensive glucose lowering strategy [5], were confirmed in further studies having recruited patients with more advanced T2D and higher CV risk but better controlled BP such as MICRO-HOPE [6] and ADVANCE-BP [7]. A recent meta-analysis by the "Blood Pressure Lowering Treatment Trialists, Collaboration" showed that lowering BP provides similar relative protection at all levels of baseline CV risk, but progressively greater absolute risk reductions as baseline risk increases [2], and it is well known that T2D markedly increases the risk of CV disease [8]. Nevertheless, even if lowering BP in patients with arterial hypertension showed a remarkable reduction in CV complications, including myocardial infarction, stroke, congestive heart failure, CV mortality and all-cause mortality, a significant interaction was detected for major CV events when trials were stratified by baseline diabetes (yes or no), with significantly larger risk reductions for populations without diabetes than in populations with diabetes [9]. It is noteworthy, however, that this interaction was not found in another meta-analysis focusing on patients at high CV risk, which rather showed a trend for slightly greater reduction in major cardiovascular events (MACEs) among patients with T2D versus patients without diabetes [10]. Finally, despite the well demonstrated benefit of lowering BP in diabetes [11], BP targets in patients with T2D [12] as well in patients with high CV risk [13] remain controverted, so that targets may vary between guidelines[14].

After the UKPDS [5], most CV outcome trials with glucose-lowering agents gave rather disappointing results [15-18]. Dipeptidyl peptidase-4 inhibitors (gliptins), which exert almost a neutral effect on BP [19], proved non-inferiority but no superiority versus placebo, demonstrating the CV safety of this pharmacological class but not its efficacy in preventing CV events [20]. Of major interest, superiority versus placebo was recently reported in EMPA-REG OUTCOME with empagliflozin [21], a sodium-glucose cotransporter type 2 (SGLT2) inhibitor that reduces arterial BP, and, to a less extent, in LEADER with liraglutide [22], a glucagon-like receptor agonist that was also associated with a modest, but significant, BP reduction.

SGLT2 inhibitors are novel glucose-lowering agents indicated for the treatment of patients with T2D [23]. These compounds have a distinct mechanism of action in the renal proximal tubule, by blocking the reabsorption of glucose. Besides promoting glucosuria, they can exert pleiotropic effects, which could reduce several CV risk factors and potentially CV complications [24, 25]. Among these pleiotropic effects, a reduction in arterial BP has been consistently reported with all SGLT2 inhibitors [26-29]. In patients with T2D and CV antecedents enrolled in the placebo-controlled EMPA-REG OUTCOME landmark trial, the addition of empagliflozin to standard care was associated with a significant reduction in the primary endpoint, a composite of CV mortality, non-fatal myocardial infarction and non-fatal stroke (so-called triple MACE) [21]. The reduction in CV mortality, which contributes to reduce all-cause mortality, was highly significant whereas no significant changes were noticed neither for myocardial infarction nor for stroke [21]. Because of the reduction in CV mortality occurred already within the first few months, concomitant with a significant reduction in hospitalization for heart failure [30], an haemodynamic rather than an anti-atherogenic effect has been suspected [31, 32]. This may be attributed to the diuretic (natriuretic/osmotic) activity of the SGLT2 inhibitor, which accompanied the glucuretic effect [33-37], although the so-called “diuretic hypothesis” has also been challenged [38, 39].

In order to analyze the potential contribution of the reduction in BP in the diminution of CV events, CV mortality and all-cause mortality reported in EMPA-REG OUTCOME [21], the literature has been scrutinized looking for randomised controlled trials (RCTs) and meta-analyses having investigated 1) the effects of SGLT2 inhibitors on BP and CV outcomes; 2) the effects of lowering BP with different antihypertensive agents, including diuretics, on CV complications and mortality in patients with T2D. To identify relevant studies, an extensive literature search in MEDLINE was performed from January 1990 to

August 2016, with the following MESH terms : T2D, BP, hypertension, diuretic, SGLT2 inhibitor, on the one hand, and CV disease, coronary heart disease, myocardial infarction, stroke, heart failure and mortality, on the other hand. No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews and meta-analyses were also carefully examined.

1) Blood pressure lowering effects of SGLT2 inhibitors

Treatment with SGLT2 inhibitors is consistently associated with a lowering of arterial BP in T2D patients with or without hypertension [26-29]. This effect has been confirmed with all SGLT2 inhibitors [29, 40] : canagliflozin [41, 42], dapagliflozin [43-45], empagliflozin [46], ertugliflozin [47] (Table 1). Generally, the reduction in systolic BP was greater (at least twofold) than the reduction in diastolic BP. The BP reduction has been demonstrated when BP was controlled in seated position in the investigator office [28, 29, 45] or during 24h-ambulatory monitoring [44-47] (Table 2). It has been suggested that circadian BP rhythm may represent a possible key target of SGLT2 inhibitors used for the treatment of Type 2 diabetes [48]. Circadian BP rhythm was maintained in these dedicated studies of SGLT2 inhibitors, with greater reductions in day-time versus night-time measurements observed for systolic BP [41, 44, 46] and diastolic BP [41, 46]. Thus circadian BP rhythm may represent a possible key target of SGLT2 inhibitors [48].

Overall, the average reduction may appear rather modest (Table 2). However, it is noteworthy that most trials with SGLT2 inhibitors were performed in T2D patients with rather well controlled BP at baseline. Post-hoc subgroup analyses have shown that greater BP reduction may be achieved in patients with higher BP levels at baseline (>140/90 mm Hg) [26, 27, 29, 49]. Canagliflozin, but not dapagliflozin and empagliflozin, showed a significant dose-response relationship with systolic BP reduction [29]. Interestingly, the reduction in BP induced by SGLT2 inhibitors is not accompanied by a significant increase in heart rate [49], arguing for an absence of sympathetic activation [50].

The BP lowering effect was also observed in patients already treated with a combination antihypertensive therapy [44], including renin-angiotensin blockers [51] or diuretics. However, the antihypertensive effect seems to be less marked when a SGLT2 inhibitor was added to a diuretic. For instance, the reduction in seated systolic BP was almost twofold lower when dapagliflozin was added to a diuretic agent than when it was added to a

beta-blocker or a calcium-channel blocker. Nevertheless, such a difference almost vanished when 24h- ambulatory SBP measurements were compared [44].

Because of their specific mechanism of action, SGLT2 inhibitors exert a lower glucose-lowering effect in patients in chronic kidney disease [52]. However, it has been demonstrated that in patients with moderate renal impairment, dapagliflozin still reduced body weight and BP while it did not improve glycemic control [53].

2) Meta-analyses of RCTs having evaluated the effects of lowering BP in patients with T2D

Several recent meta-analyses investigated the effects of lowering BP with different antihypertensive agents on CV outcomes in patients with T2D (Table 2) [9, 54-56]. In all these studies, results are expressed as standardised effects of a 10 mm Hg reduction in systolic BP. All meta-analyses showed significant reductions in CV composite endpoints (MACEs), myocardial infarction, stroke and congestive heart failure (Table 2). All meta-analyses also reported a significant reduction in all-cause mortality. However, and surprisingly, only one meta-analysis reported data on CV mortality and it failed to demonstrate a significant reduction although a trend for better prognosis was observed (odds ratio or OR = 0.92; confidence interval or CI 95% 0.82-1.03) [56].

Most trials with antihypertensive agents have been performed in T2D patients with high BP at baseline, especially the UKPDS [4]. In contrast, baseline BP of T2D patients in EMPA-REG OUTCOME was rather well controlled, below 140/90 mm Hg on average [21]. Therefore, it is interesting to analyze the influence of baseline BP on the effects of lowering BP on CV outcomes in T2D patients with hypertension (Table 2). In two meta-analyses which separated the whole population into two subgroups (high versus low baseline systolic BP), the reductions in major CV events, myocardial infarction, stroke, CV mortality and all-cause mortality were significantly greater in patients with the higher systolic BP whereas such reductions, if present, were rather modest and not statistically significant in patients with the

lower systolic BP at baseline (Table 2) [54, 56]. These observations were confirmed in another meta-analysis focusing on stroke (Table 2) [55]. The only disturbing results were reported in a meta-analysis which divided the whole population into 5 categories according to baseline systolic BP, from < 130 mm Hg to ≥160 mm Hg (Table 2) [9]. In this latter more sophisticated analysis, the influence of systolic BP at baseline did not appear clearly and CV protection was also present in T2D patients with systolic BP < 130 or 140 mm Hg at baseline (Table 2).

3) Trials with different BP targets in patients with T2D

BP targets in patients with T2D are controverted because results from RCTs were heterogeneous [12]. In the Hypertension Optimal Treatment (HOT) trial, 18 790 patients were randomly assigned a target diastolic BP ≤ 80, ≤ 85 or ≤ 90 mm Hg [57]. The lowest incidence of major CV events occurred at a mean achieved diastolic BP of 82.6 mm Hg and the lowest risk of CV mortality occurred at 86.5 mm Hg. In the subgroup of 1501 patients with T2D at baseline, a decline in the rate of major CV events was seen in relation to the target group (P for trend=0·005). In the group randomised to diastolic BP ≤ 80 mm Hg the risk of major CV events was almost halved in comparison with that of the target group ≤ 90 mm Hg. Interestingly, the difference was greater in diabetic than in nondiabetic patients [57]. The approximate halving of the risk was also observed for myocardial infarction, although it was not significant. Stroke also showed a declining rate with lower target BP groups, with a risk reduction of about 30% in the ≤ 80 mm Hg target group *versus* ≤ 90 mm Hg target group. CV mortality was also significantly lower in the ≤ 80 mm Hg target group than in each of the other target groups ≤ 85 or ≤ 90 mm Hg, but these results should be taken with caution because of a rather low number of events (Table 3) [57].

In a large RCT in T2D patients at high CV risk ((Action to Control Cardiovascular Risk in Diabetes, ACCORD-BP) [58], targeting a systolic BP of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major CV events. No reduction was observed regarding myocardial infarction, heart failure, CV mortality and all-cause mortality. The only significant reduction concerned stroke (-41%, P = 0.01) (Table 3).

To evaluate the effects of achieved systolic BP during antihypertensive treatment on CV outcomes, event rates of a composite primary endpoint (CV death or nonfatal myocardial infarction or stroke) at on-treatment systolic BP of ≥ 140 mm Hg and the 10 mm Hg intervals

of <140 mm Hg, <130 mm Hg, and <120 mm Hg were measured in 6459 patients with diabetes and 4246 patients without diabetes from the ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension) substudy [59] . In the diabetic cohort (6459 patients), the primary endpoint was 49% lower ($P < 0.001$) at <140 mm Hg than at ≥ 140 mm Hg, and the separate components of this endpoint were also significantly reduced (Table 3). Further systolic BP reductions did not improve outcomes, and at <120 mm Hg they were no longer different (except for stroke : -56%, $P = 0.0120$) from ≥ 140 mm Hg [59].

In contrast, in the nondiabetic cohort, the primary endpoint event rate fell steadily (although not significantly) through the decreasing systolic BP categories until it was reduced by 45% ($P = 0.0413$) at <120 mm Hg. Total stroke rate was lowest at <120 mm Hg (-68%, $P = 0.0067$) [59]. These results in patients at high risk for CV events but without diabetes were confirmed in the recent SPRINT trial [60]. In the latter study, targeting a systolic BP of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major CV events, heart failure, CV mortality and death from any cause [60] (Table 3).

According to a meta-analysis of RCTs published in 2005, there was limited evidence that lower BP goals produce larger reductions in total MACEs in individuals with versus without diabetes, and the short- to medium-term effects on MACEs of various BP-lowering regimens studied in the literature were broadly comparable for patients with and without diabetes [61]. At the present time, evidence from RCTs does not support BP targets lower than the standard targets in people with elevated BP and T2D [12]. On the contrary, taken altogether, available results rather suggest that T2D patients (<140 mm Hg or <130 mm Hg) and nondiabetic patients (<120 mm Hg) may require different systolic BP targets for optimal CV protection, although stroke and renal considerations should also influence the selection of BP targets [62].

4) Cardiovascular outcome results in EMPA-REG OUTCOME vs other major RCTs with antihypertensive agents in patients with T2D

The first landmark study in patients with T2D was the UKPDS study [4]. This trial recruited patients with newly diagnosed T2D. BP was rather high at baseline and patients were randomly assigned to an antihypertensive therapy (captopril or atenolol) or placebo. The

average reduction in systolic BP reached 10 mm Hg. This was associated with a significant reduction in CV events, stroke and CV mortality. The reduction in myocardial infarction and all-cause mortality did not reach statistical significance (Table 4). These results are in agreement with those reported in meta-analyses having studied the effects of a 10 mm Hg systolic BP reduction in patients with T2D (see comment above and table 2). However, it is quite hazardous to compare the results of EMPA-REG OUTCOME with those of UKPDS. Indeed, in the UKPDS, in contrast to EMPA-REG OUTCOME, patients were not selected upon CV antecedents and did not receive standard therapy to reduce CV risk throughout the study, the initial BP was higher, the treatment-associated BP drop was greater, and the duration of the follow-up was much longer.

In this regard, MICRO-HOPE [6] and ADVANCE-BP [7] are other major placebo-controlled trials with characteristics closer to those of EMPA-REG OUTCOME because they recruited T2D patients who were aged 55 years or older, and who had a history of CV disease or at least another CV risk factor. Both studies tested the effects of blocking the renin-angiotensin system with an ACE inhibitor, either alone (enalapril in MICRO-HOPE) [6] or in combination with a diuretic (fixed combination of perindopril and indapamide in ADVANCE-BP) [7]. In both trials, baseline BP levels were only slightly above those in EMPA-REG-OUTCOME and the average BP reduction with the antihypertensive therapy was in the same order of magnitude (Table 4). After a mean follow-up of around 4-5 years, reductions in composite CV events, myocardial infarction, stroke, heart failure, CV mortality and all-cause mortality were observed in both MICRO-HOPE and ADVANCE-BP. The CV protection observed in EMPA-REG OUTCOME trial appears almost similar to that reported in these two trials (Table 4). One major difference, however, is that a large majority (81%) of patients in EMPA-REG OUTCOME were already treated with a blocker of the renin-angiotensin system combined with other CV protective agents (statins, antiplatelet compounds, …) [21]. Thus empagliflozin provided an additional protection in T2D patients with antecedents of CV disease but already receiving optimal standard therapy. The presence of T2D and previous CV disease markedly increases the risk of recurrent CV events and thus should increase the absolute benefit resulting from a lowering of BP [2]. This high CV risk at baseline might be of importance. Indeed, a recent trial showed that therapy with candesartan plus hydrochlorothiazide was not associated with a lower rate of major CV events than placebo among persons at intermediate risk (at least one CV risk factor among which dysglycaemia but not T2D) who did not have known CV disease [63].

5) Meta-analyses of trials with cardiovascular outcome results : comparison between diuretic agents and SGLT2 inhibitors

The mode of action of empagliflozin targeting the kidney may mimic that of a diuretic and a "diuretic hypothesis" has been put forward to explain the early and marked CV protection in EMPA-REG OUTCOME [33-37]. Therefore, the comparison of the CV effects of empagliflozin in EMPA-REG OUTCOME with those of different diuretics deserves further attention. A recent network meta-analysis of studies with both placebo-treated or untreated controls and with actively treated controls analyzed health outcomes associated with various antihypertensive therapies used as first-line agents in the general population. It concluded that low-dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality [64]. Furthermore, reduction in arterial BP is very effective in preventing heart failure and diuretics may be superior to other antihypertensive therapies in this respect [65]. Thiazide diuretics, including thiazide-type (chlorothiazide and hydrochlorothiazide) and thiazide-like diuretics (indapamide and chlorthalidone), have been used for the treatment of hypertension for more than 5 decades and are still the most popular diuretics. Even it has been suggested to use more diuretics to attain target BP in diabetic hypertensive patients [66, 67], available results in patients with T2D are scarce and largely incomplete. As an example, three meta-analyses investigating the effects of thiazides and thiazide-like diuretics on CV outcomes did not mention the diabetic population (Table 5) [64, 68, 69]. Overall, the reduction in CV events mainly concerned stroke and heart failure whereas the effects on myocardial infarction and coronary events was less pronounced and generally not statistically significant. The reduction in mortality averaged 10 to 20 % and was borderline significant. In contrast to has been reported in one meta-analysis [55], another meta-analysis [68] suggested that thiazide-like diuretics have greater protective effect against CV events than thiazide-type diuretics, especially on heart failure.

Table 5 summarizes results published in a few meta-analyses focusing on the effects of different diuretics, mainly thiazides in patients with T2D patients with hypertension [70, 71] and mineralocorticoid receptor antagonists in T2D patients with heart failure [72-74] (no such available data for loop diuretics in T2D patients). These results were compared with results reported in two meta-analyses assembling data obtained with SGLT2 inhibitors in T2D patients (all patients not selected for the presence of hypertension or heart failure) [75, 76] (Table 5). Overall, SGLT2 inhibitors gave at least similar or in most instances better results as

compared to classic diuretics, whatever the outcome considered (Table 5). Strokes represent the only exception, because they were significantly reduced whereas a trend to a modest increase was reported with SGLT2 inhibitors, a finding mainly driven by the results of EMPA-REG OUTCOME [21].

As previously discussed, available data do not support a major contribution of the diuretic effect of empagliflozin in the reduction in CV and all-cause mortality in EMPA-REG OUTCOME, even if conclusions drawn from indirect comparison require caution [38, 39].

6) Post-hoc analyses of EMPA-REG OUTCOME

The protective effect of empagliflozin was observed independently of the baseline level of BP : CV mortality : HR = 0.56 (0.40, 0.79) in patients with systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg vs HR = 0.67 (0.50, 0.91) in patients with systolic BP < 140 mmHg and/or diastolic BP <90 mmHg [21]. Whereas the use of lipid-lowering agents and antiplatelet/anticoagulant agents was similar in patients receiving empagliflozin or placebo throughout the study, the use of antihypertensive agents was less pronounced in patients treated with empagliflozin than in those receiving placebo [21]. This imbalance may contribute to dampen the difference in BP between the two groups. Subgroups analyses comparing CV outcomes in T2D patients with marked versus modest reduction in BP with empagliflozin therapy would be of great interest to further appreciate the role of BP lowering in the overall CV protection but this information is not available yet.

Subgroup analyses suggest that the background antihypertensive therapy does not significantly alter the effect of empagliflozin. The vast majority of participants in the EMPA-REG OUTCOME study were treated with drugs inhibiting the renin-angiotensin system. It has been postulated that in patients treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, empagliflozin could have had additive cardioprotective effects through the activation of non-classic renin-angiotensin system pathways, i.e. activation of the AT2 receptor and the Angiotensin 1–7 pathway, with an anti-proliferative, anti-inflammatory, anti-arrhythmic, vasodilatory effect [77].

Almost one third of patients participating to EMPA-REG OUTCOME had impaired renal function with an estimated glomerular filtration rate < 60 ml/min/m² (eGFR = 48.4 ml/min/m²) and a prespecified analysis compared them with patients with normal kidney function (eGFR = 83.1 ml/min/m²) [21, 78]. Patients with renal impairment had rather similar

baseline BP control as patients with normal kidney function (136.1/74.5 mm Hg versus 135.0/77.4 mm Hg, respectively), but received more antihypertensive agents, especially diuretics (58.6 % vs 38.5% of patients, respectively). Incident or worsening nephropathy or cardiovascular death was significantly reduced with empagliflozin compared with placebo in patients with prevalent kidney disease defined as eGFR <60 mL/min/1.73m² and/or macroalbuminuria at baseline (HR = 0.64; 95% CI 0.53, 0.76; P <0.001) [21, 78]. Thus cardiorenal protection appears to be of the same magnitude in patients at high risk of CV disease with chronic kidney disease at baseline as in those without renal impairment.

Finally, there was no reduction in stroke in EMPA-REG OUTCOME (a non-significant increase was even reported, partially driven by the occurrence of cerebrovascular events within the month following treatment interruption) whereas antihypertensive agents, and especially diuretics, are known to be particularly effective in preventing stroke in hypertensive patients [66]. Thus, the absence of reduction in stroke (and possibly an increased risk) in EMPA-REG OUTCOME is surprising. However, these results may be explained by the rather good BP control at baseline in the population of EMPA-REG-OUTCOME [21]. Indeed, at least two meta-analyses having investigated the influence of baseline BP on CV outcomes suggest that the reduction in the incidence of stroke by antihypertensive therapies were no longer significant in T2D patients with baseline systolic BP < 140 mm Hg (see table 2) [55, 56], which was the case in EMPA-REG OUTCOME [21].

Conclusion

EMPA-REG OUTCOME reported a marked reduction in CV mortality and all-cause death rate with the SGLT2 inhibitor empagliflozin, together with a significant reduction in hospitalization for heart failure, in T2D patients with antecedents of CV disease. Obviously, these results cannot be explained by the modest improvement in glucose control. SGLT2 inhibitors induce a consistent BP reduction although the contribution of this effect to the better CV outcomes is unclear. A CV protection has also been reported with various antihypertensive agents but generally in patients with higher BP at baseline and showing a greater reduction in BP as compared to patients of EMPA-REG OUTCOME. Although a diuretic hypothesis has been proposed to explain most of the benefit, comparison with available data published with classic diuretics, especially thiazides, does not allow to fully support this hypothesis. Thus, although BP reduction associated to empagliflozin therapy may partly contribute to the benefits reported in EMPA-REG OUTCOME, other mechanisms most

probably play a greater role in the overall CV protection and reduction in mortality observed in this trial.

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Table 1 : Effects of SGLT2 inhibitors on arterial systolic and diastolic blood pressure.

Trials/ SGLT2 inhibitors	Reference	N Period of the day	Changes in systolic BP mm Hg			Changes in diastolic BP mm Hg		
			Point estimate	Lower 95% CI limit	Upper 95% CI limit	Point estimate	Lower 95% CI limit	Upper 95% CI limit
All trials in T2D patients with or without hypertension (investigator office blood pressure measurement) Placebo-subtracted changes								
All SGLT2	Baker et al 2014 [29]	12960	-3.96	-4.41	-3.51	-1.59	-2.18	-1.01
Placebo controlled RCTs		7875	-3.82	-4.40	-3.23	-1.45	-1.81	-1.08
Active controlled RCTs		5085	-4.17	-4.88	-3.46	-1.87	-2.33	-1.40
Canagliflozin		5607	-4.38	-5.08	-3.69	-2.02	-2.48	-1.56
Dapagliflozin		5280	-3.78	-4.49	-3.07	-1.41	-1.86	-0.96
Empagliflozin		1359	-3.02	-4.25	-1.80	-1.01	-1.72	-0.31
Ipragliflozin		679	-3.65	-5.98	-1.31	-1.78	-3.52	-0.04
Placebo-controlled RCTs	Zaccardi et al 2016 [40]							
Canagliflozin 100 mg		7853	-3.89	-4.90	-2.88	-1.64	-2.25	-1.03
Canagliflozin 300 mg			-4.87	-5.87	-3.87	-2.03	-2.63	-1.44
Dapagliflozin 5 mg		7681	-2.84	-4.14	-1.54	-1.53	-2.48	-0.59
Dapagliflozin 10 mg			-3.01	-3.89	-2.13	-1.74	-2.58	-0.89
Empagliflozin 10 mg		8463	-3.33	-4.25	-2.41	-1.65	-2.20	-1.10
Empagliflozin 25 mg			-3.66	-4.54	-2.77	-1.91	-2.44	-1.38
Trials in T2D patients with hypertension (24h-ambulatory blood pressure monitoring) Placebo-subtracted changes								
Canagliflozin	100 mg Townsend et al 2016 [41]	57 vs 56 24-h	-3.3	-6.7	+0.2	-1.9	-4.0	+0.1
		Daytime	-4.0	-7.5	-0.5	-2.2	-4.3	-0.1
		Nighttime	-0.9	-5.1	3.3	-2.4	-4.9	0.2
	300 mg Townsend et al 2016	56 vs 56 24-h	-4.9	-8.4	-1.5	-2.9	-5.0	-0.9

	[41] Daytime Nighttime	Daytime	-5.4	-8.9	-1.9	-3.0	-5.0	-0.9
		Nighttime	-3.0	-7.2	1.1	-0.8	-3.4	1.8
Dapagliflozin	10 mg Lambers Heerspink et al 2013 [43] (*)	25 vs 24 24-h	-5.6	-10.3	-1.0	NA	NA	NA
		Daytime	-8.8	-13.7	-3.9	NA	NA	NA
		Nighttime	-6.0	-11.1	-1.0	NA	NA	NA
	10 mg Weber et al 2016 [44]	187 vs 186 24-h	-4.45	-7.14	-1.76	NA	NA	NA
		Daytime	-4.76	-7.52	-2.0	-1.86	-3.64	-0.08
		Nighttime	-3.88	-6.85	-0.90	-2.11	-4.00	-0.23
Empagliflozin	10 mg Tikkanen et al 2015 [46]	276 vs 271 24-h	-3.44	-4.78	-2.09	-1.36	-2.15	-0.56
		Daytime	-3.94	-5.37	-2.52	-1.56	-2.42	-0.69
		Nighttime	-2.50	-4.09	-0.91	-0.95	-1.93	0.03
	25 mg Tikkanen et al 2015 [46]	276 vs 271	-4.16	-5.50	-2.83	-1.72	-2.51	-0.93
		Daytime	-4.78	-6.20	-3.36	-1.98	-2.84	-1.12
		Nighttime	-2.90	-4.48	-1.32	-1.15	-2.12	-0.18
Ertugliflozin	5 mg Amin et al 2015 [47] (**)	38 vs 38 24-h	-3.93	-6.10	-1.76	-3.09	-4.53	-1.65
		Daytime	-4.34	-6.67	-2.01	-2.69	-4.19	-1.18
		Nighttime	-3.18	-6.06	-0.30	-3.55	-5.58	-1.51
	25 mg Amin et al 2015 [47] (**)	39 vs 38	-3.62	-5.71	-1.54	-2.24	-3.63	-0.86
		Daytime	-4.89	-7.14	-2.65	-2.58	-4.03	-1.13
		Nighttime	-2.02	-4.79	0.74	-1.87	-3.82	0.09

BP : blood pressure. NA not available

(*) Results expressed as absolute changes rather than placebo-subtracted changes

(**) Results giving 80 % CI instead of 95 % CI because it was a Phase 2 study

Table 2 : Recent meta-analyses of randomised controlled trials having investigated the effects of lowering blood pressure (all antihypertensive agents combined) on cardiovascular outcomes in patients with hypertension and type 2 diabetes and the influence of baseline blood pressure. Results are expressed as standardised effects of a 10 mm Hg reduction in systolic blood pressure (mean hazard ratio with 95% confidence interval and P value).

Meta-analyses	Baseline systolic blood pressure (mm Hg)	Primary composite CV endpoints	Myocardial infarction	Stroke	CV mortality	All-cause mortality	Congestive heart failure
Emdin et al 2015 [54]	Pooled data (any BP level	0.89 (0.83-0.95)	0.88 (0.80-0.98)	0.73 (0.64-0.83)	NA	0.87 (0.78-0.96)	0.86 (0.74-1.00)
	≥ 140	0.74 (0.65-0.85)	0.73 (0.61-0.87)	0.74 (0.64-0.86)	NA	0.73 (0.64-0.84)	0.75 (0.59-0.94)
	< 140	0.96 (0.88-1.05)	0.97 (0.86-1.10)	0.69 (0.52-0.92)	NA	1.07 (0.92-1.26)	0.97 (0.79-1.19)
Ettehad et al 2016 [9]	Pooled data (any BP level)	0.80 (0.77-0.83)	0.83 (0.78-0.88)	0.73 (0.68-0.77)	NA	0.87 (0.84-0.91)	0.72 (0.67-0.78)
	<130	0.63 (0.50-0.80)	0.55 (0.42-0.72)	0.65 (0.27-1.57)	NA	0.53 (0.37-0.76)	0.83 (0.41-1.70)
	130-139	0.87 (0.82-0.92)	0.88 (0.80-0.96)	0.73 (0.62-0.85)	NA	0.89 (0.82-0.98)	0.75 (0.66-0.85)
	140-149	0.79 (0.72-0.87)	0.80 (0.69-0.94)	0.78 (0.70-0.87)	NA	0.99 (0.89-1.09)	0.83 (0.70-1.00)
	150-159	0.80 (0.71-0.91)	0.84 (0.68-1.05)	0.65 (0.54-0.78)	NA	0.78 (0.69-0.90)	0.96 (0.71-1.30)
	≥160	0.74 (0.69-0.79)	0.82 (0.73-0.92)	0.70 (0.64-0.78)	NA	0.86 (0.80-0.92)	0.61 (0.54-0.70)
Brunström et al 2016 [56]	Pooled data (any BP level)	NA	0.87 (0.81 to 0.94)	0.87 (0.79 to 0.96)	0.92 (0.82-1.03)	0.92 (0.87 to 0.96)	0.82 (0.75 to 0.89)
	> 150	NA	0.74 (0.63-0.87)	0.77 (0.65-0.91)	0.75 (0.57-0.99)	0.89 (0.80-0.99)	0.73 (0.53-1.01)
	140-150	NA	0.84 (0.76-	0.92 (0.83-	0.87 (0.71-	0.87 (0.78-	0.80 (0.66-

			0.93)	1.01)	1.05)	0.98)	0.97)
	< 140	NA	1.00 (0.87-1.15)	0.81 (0.53-1.22)	1.15 (1.00-1.32)	1.05 (0.95-1.16)	0.90 (0.79-1.02)
Xie et al 2016 [55]	Pooled data (any BP level)	NA	NA	0.74 (0.66-0.83)	NA	NA	NA
	≥ 140	NA	NA	0.71 (0.63-0.80)	NA	NA	NA
	< 140	NA	NA	0.90 (0.69-1.17)	NA	NA	NA

CV : cardiovascular. NA : not available.

Table 3 : Comparison of cardiovascular outcome results in clinical trials with different blood pressure targets in patients with T2D.

Trials Patients	Intervention	Patients n Intensive vs less intensive	Duration of follow-up Years	Baseline BP mm Hg	Achieved BP mm Hg	Composite CV events	MI	Stroke	CV mortality	All-cause mortality	Heart failure
Targeting diastolic BP											
HOT [57] Patients with T2D (subgroup)	Diastolic BP ≤ 90 versus ≤ 85 mm Hg	501 vs 501	3.8	170/105	143.7/ 85.2 vs 141.4/ 83.2	1.32 (0.84-2.06)	1.75 (0.73-4.17)	1.30 (0.63-2.67)	0.99 (0.54-1.82)	1.03 (0.62-1.71)	NA
	Diastolic BP ≤ 90 versus ≤ 80 mm Hg	501 vs 489			143.7/ 85.2 vs 139.7/81.1	2.06 (1.24-3.44)	2.01 (0.81-4.97)	1.43 (0.68-2.99)	3.0 (1.28-7.08)	1.77 (0.98-3.21)	NA
Targeting systolic BP											
ACCORD [58] Patients with T2D	Systolic BP < 120 versus < 140 mm Hg	2362 vs 2371	4.7	139/76	119.3/ 64.4 vs 133.5/ 70.5	0.88 (0.73-1.06) 0.20	0.94 (0.79-1.12) P=0.50	0.59 (0.39-0.89) P= 0.01	1.06 (0.74-1.52) P=0.74	1.07 (0.85-1.35) P=0.55	0.94 (0.70-1.26) P= 0.67
ACCOMPLISH [59] Patients with T2D (subgroup)	Systolic BP 130-<140 vs ≥ 140 mm Hg	2003 vs 1429	3.0	145.7/ 79.5	134.4/74.1 vs 150.4/78.1	0.51 (0.39-0.68)	0.50 (0.34-0.75)	0.50 (0.32-0.80)	0.46 (0.28-0.77)	NA	NA
	Systolic BP 120-<130 vs ≥ 140 mm Hg	2224 vs 1429			125.5/71.5 vs 150.4/78.1	0.46 (0.35-0.61)	0.34 (0.22-0.53)	0.62 (0.41-0.95)	0.48 (0.30-0.79)	NA	NA
	Systolic BP 110-<120 vs	803 vs 1429			116.3/67.8 vs	0.66 (0.46-0.93)	0.72 (0.45-	0.44 (0.23-	0.78 (0.44-	NA	NA

	≥ 140 mm Hg				150.4/78.1		1.16)	0.85)	1.39)		
SPRINT [60] Patients at high CV risk but without T2D	Systolic BP < 120 versus < 140 mm Hg	4678 vs 4683	3.3	140/78	121.5/ 68.7 vs 134.6/76.3	0.75 (0.64-0.89)	0.83 (0.64-1.09)	0.89 (0.63-1.25)	0.57 (0.38-0.85)	0.73 (0.60-0.90)	0.62 (0.45-0.84)

BP : blood pressure. MI : myocardial infarction. NA : not available

Table 4 : Comparison of cardiovascular outcome results in EMPA-REG OUTCOME and other major trials having evaluated an antihypertensive therapy in patients with T2D.

	Intervention	Patients n Active vs placebo	Duration of follow-up Years	Baseline BP mm Hg	Delta BP vs placebo mm Hg	Composite CV events	MI or coronary events	Stroke	CV mortality	All-cause mortality	Heart failure
UKPDS [4]	Captopril or atenolol	758 vs 390	8.4	159/94	10/5	0.66 (NA) P=0.019	0.79 (0.59-1.07) P=0.13	0.56 (0.35-0.89) P=0.013	0.68 (0.49-0.94) (*) P=0.019	0.82 (0.63-1.08) P=0.17	NA
MICRO-HOPE [6]	Enalapril	1808 vs 1769	4.5	142/80	2.5/1	0.75 (0.64-0.88) P = 0.0004	0.78 (0.64-0.96)	0.67 (0.50-0.90)	0.63 (0.49-0.79)	0.76 (0.63-0.92)	NA
ADVANCE [7]	Perindopril-indapamide	5569 vs 5571	5.3	145/81	5.6/2.2	0.92 (0.81-1.04) P=0.16	0.86 (0.76-0.98) P=0.020	0.94 (0.80-1.10) P=0.42	0.82 (0.68-0.98) P=0.027	0.86 (0.75-0.98) P=0.025	0.98 (0.81-1.20) P=0.86
EMPA-REG OUTCOME [21]	Empagliflozin	4687 vs 2333	3.1	135.3/76.6	~ 4/1	0.86 (0.74-0.99) P = 0.04	0.87 (0.70-1.09) P = 0.22	1.24 (0.92-1.67) P = 0.16	0.62 (0.49-0.77) P < 0.001 (***)	0.68 (0.57-0.82) P <0.001	0.65 (0.50-0.85) (**) P < 0.001

(*) Mortality related to diabetes rather than CV mortality

(**) Hospitalisation for heart failure

(***) HR = 0.56 (0.40, 0.79) in patients with baseline SBP ≥ 140 and/or DBP ≥ 90 mm Hg vs HR = 0.67 (0.50, 0.91) in patients with baseline SBP < 140 and DBP < 90 mm Hg

Table 5 : Comparison of cardiovascular outcome results in meta-analyses of trials with diuretics and with SGLT2 inhibitors.

Trials	T2D patients	Intervention	BP reduction mm Hg	Composite CV events	Myocardial infarction	Stroke	CV mortality	All-cause mortality	Heart failure
Meta-analyses in a general population									
Psaty et al 2003 [64]	Hypertension	Diuretics vs placebo	-13.2/ -4.9	0.76 (0.69-0.83) P = NA	0.79 (0.69-0.92) P = NA	0.71 (0.63-0.81) P = NA	0.81 (0.73-0.92) P = NA	0.90 (0.84-0.96) P = NA	0.51 (0.42-0.62
Chen et al 2015 [68]	Hypertension	Thiazide-type and thiazide-like vs placebo	NA	0.86 (0.77-0.96) *P* = 0.007)	0.95 (0.85-1.06) *P* = 0.378)	0.92 (0.75-1.13) *P* = 0.438	NA	NA	0.62 (0.49-0.79) *P* < 0.001)
		Thiazide-type vs placebo	-22.7/ -11.8	0.92 (0.79-1.07) *P* = 0.278)	0.96 (0.78-1.19) *P* = 0.725)	1.03 (0.67-1.56) *P* = 0.907	NA	NA	0.71 (0.44-1.15) *P* = 0.161
		Thiazide-like vs placebo	-14.4/ -8.3	0.78 (0.68-0.90) *P* < 0.001),	0.98 (0.91-1.05) *P* = 0.565	0.82 (0.70-0.96) *P* = 0.016).	NA	NA	0.57 (0.43-0.76) *P* < 0.001)
Olde Engberink et al 2015 [69]	Hypertension	Thiazide-type vs placebo	-14.5/ -6.7	0.67 (0.56-0.81)	0.81 (0.63-1.05)	0.52 (0.38-0.69)	NA	0.86 (0.75-1.00)	0.36 (0.16-0.84)
		Thiazide-like vs placebo	-13.0/ -4.6	0.67 (0.60-0.75)	0.76 (0.61-0.96)	0.68 (0.57-0.80)	NA	0.84 (0.74-0.96)	0.47 (0.36-0.61)
Meta-analyses in a population with T2D									
Lièvre et al 2000 [70]	Hypertension	HCT vs placebo	-11.0/ -4.4	0.80 (0.66-9.98) *P* = 0.032	0.85 (0.65 to 1.11) P = 0.23	0.637 (0.45-0.90) P = 0.011	0.85 (0.64-1.13) P = 0.27	0.952 (0.82-1.23) P = 0.65	NA
Remonti et al 2016 [71]	Hypertension	Thiazide vs placebo	-3.38/-1.07	NA	NA	NA	0.85 (0.24-2.79) NS	0.98 (0.72-1.32) NS	NA
Chen et al 2016 [73]	Congestive heart failure	Spironolactone/ eplerenone vs	NA (a)	NA	NA	NA	0.83 (0.70-0.98)	0.78 (0.69-0.88)	0.73 (0.52-1.01)

		placebo					P = 0.04	P< 0.0001	
Wu et al 2016 [75]	All types	All SGLT2i versus all comparators	NA (b)	0.84 (0.75-0.95) P = 0.006	0.88 (0.72-1.07) P = 0.18	1.30 (1.00-1.68) P =0.049	0.63 (0.51-0.77) P < 0.0001	0.71 (0.61-0.83) P < 0.0001	0.65 (0.50-0.85)
Monami et al 2016 [76]	All types	All SGLT2i versus all comparators	NA (b)	NA	0.77 (0.63-0.94) P < 0.01	1.09 (0.86-1.38) P = 0.50	0.43 (0.36-0.53) P < 0.001	0.70 (0.59-0.83) P < 0.001	NA

CV : cardiovascular. NA : not available. HCT : hydrochlorothiazide. SGLT2i : SGLT2 inhibitors.T2D : type 2 diabetes

(a): Not available but data reported in other meta-analyses : Spironolactone : reduction in systolic/diastolic BP : -9.4/-3.8 mm Hg [72] in patients with arterial hypertension. Eplerenone : reduction in systolic/diastolic BP: -8.07/-4.08 in patients with mild to moderate hypertension [74].

(b) Not available but data reported in other meta-analyses Hg (see meta-analysis by Baker et al in Table 1 [29]): reduction in systolic/diastolic BP : -3.96/-1.59 mm Hg.

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Highlights

- Empagliflozin reduces mortality in diabetic patients with cardiovascular disease.
- A reduction in blood pressure could contribute to better outcomes with empagliflozin.
- Empagliflozin improves prognosis more than did antihypertensive agents (diuretics).
- Other mechanisms should explain the cardiovascular protection in EMPA-REG OUTCOME.