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REVIEW

Management of Diabetes and Hypertension within the Gulf Region: Updates on Treatment Practices and Therapies

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ABSTRACT

Cardiovascular disease (CVD) is a leading cause of death globally, driven by the high rates of risk factors, such as diabetes and hypertension. As the prevalence of these risk factors is particularly high in the Gulf region, better diagnosis and management of type 2 diabetes (T2D) and hypertension has the potential to dramatically reduce adverse cardiovascular outcomes for individuals in that part of the world. This article provides a summary of presentations made during the EVIDENT summit, a virtual symposium on Evidence in Diabetes and Hypertension, held in September 2021, including a review of the various guidelines for both T2D and hypertension, as well as recent findings

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relevant to the safety and efficacy for therapies relating to these conditions. Of relevance to the Gulf region, the risk of hypoglycaemia with sulfonylureas during Ramadan was reviewed. For the management of T2D, sulfonylureas have been a long-standing medication used to achieve glycaemic control; however, differences have emerged between early and later generations, with recent studies suggesting improvements in the safety profiles of late-generation sulfonylureas. For patients with hypertension, incremental therapy changes are recommended to reduce the risk of cardiovascular complications that are associated with increasing blood pressure. For first-line therapy, angiotensin-converting enzyme inhibitors (ACEi), such as perindopril, have been demonstrated to reduce the risk of cardiovascular and all-cause mortality. The addition of calcium channel blockers and diuretics to ACEi has been shown to be effective in patients with poorly controlled hypertension. The different renin–angiotensin–aldosterone system inhibitors are reviewed, and the benefit of combination therapies, including amlodipine and indapamide in patients with difficult-to-control hypertension, is investigated. The benefits of lifestyle modifications for these patients are also discussed, with important clinical considerations that are expected to inform patient management in daily clinical practice.

Keywords: Amlodipine; Gliclazide MR; Guidelines; Hypertension; Indapamide; Perindopril; Ramadan; Sulfonylureas; Type 2 diabetes

Key Summary Points

The prevalence of hypertension and diabetes within the Gulf region is high.

Sulfonylureas are a common choice of second-line therapy, particularly as part of combination therapy.

Of the sulfonylureas available, gliclazide modified release is associated with a low rate of hypoglycaemia, does not increase the risk of developing cardiovascular complications and has proven renal benefits.

Angiotensin-converting enzyme inhibitors are associated with fewer cardiovascular safety complications than angiotensin receptor blockers in patients with hypertension, and single-pill combinations improve adherence for patients with hypertension.

INTRODUCTION

Diabetes is a chronic, progressive disease that is associated with high morbidity and mortality, and a substantial proportion of the diabetic population also have hypertension [1–3]. Sulfonylureas (SUs) are still one of the most commonly prescribed anti-diabetic therapies, and within the Eastern Mediterranean region, the combination of metformin and SU account for 23.9% of first-line prescriptions [4, 5]. Since their introduction as an anti-diabetic therapy in the 1960s, different generations of SU have been developed, with differences in absorption and

Table 1 Aggregate outcomes at the 10-year follow-up of patients who underwent intensive glucose control with sulfonylurea and insulin. Adapted from *N Engl J Med*. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. 359(15):1577–89 [31]. Copyright © 2008 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Aggregate endpoint	Patients with clinical outcomes, *n*		Relative risk reduction at follow-up (95% CI)
	Intensive therapy (*N* = 2729)	Conventional therapy (*N* = 1138)	
Any diabetes-related endpoint	1571	686	9% (0.040)
Microvascular disease	429	222	24% (0.001)
Myocardial infarction	678	319	15% (0.01)
All-cause mortality	1162	537	13% (0.007)

CI confidence interval

metabolism, as well as interactions with SUR1 and SUR2 receptors, noted between agents [6].

Hypertension is a highly prevalent condition that significantly increases a patient's risk of developing cardiovascular disease (CVD), the leading cause of death from non-communicable causes globally [3]. For the treatment of hypertension, renin–angiotensin–aldosterone system inhibitors (RAASis) are the most widely prescribed class of drugs, including angiotensin-converting enzyme inhibitors (ACEis) and angiotensin-receptor blockers (ARBs), the two most clinically relevant anti-hypertensive agents [7–12]. While RAASi are generally prescribed as a first-line therapy, poorly controlled hypertension is often managed with the addition of calcium channel blockers (CCBs) and diuretics [13].

Given the high prevalence of both T2D and hypertension within the Gulf region, optimal management of patients with these conditions is essential to prevent cardiovascular morbidity and mortality. The current article describes several presentations made during the EVIDENT summit, a virtual symposium on Evidence in Diabetes and Hypertension, held in September 2021. These presentations examine current recommendations and evidence for the management of type 2 diabetes (T2D) and hypertension. Specifically, for patients with uncontrolled hypertension, current guidelines were reviewed and strategies for effective blood pressure (BP) control were investigated, along with efficacy and safety data for different classes of anti-hypertensives. In addition, the value of target glycaemic control in patients with diabetes was explored and safety data for early- and later-generation SU were evaluated. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

ESTABLISHING EARLY GLYCAEMIC CONTROL IN PATIENTS WITH DIABETES

Diabetes within the Gulf Region

The prevalence of diabetes in the Gulf region is high; for example, it was reported at 15% in the United Arab Emirates (UAE) in a recent study in Dubai (19% for Emirati and 14.7% for non-Emirati people), with higher rates observed in men than in women (17.8% and 11.5%, respectively) [14]. Notably, 10.8% of the study population were newly diagnosed individuals with diabetes [14]. Increasing age was associated with increased rates of diabetes, as the prevalence was 43.7% in those aged $\geq$ 60 years. When comparing the prevalence of diabetes in Dubai with the wider Gulf region, the reported prevalence of diabetes in those above 30 years of age is 25.4% in Saudi Arabia, 18.8% in Kuwait and 16.7% in Qatar [15–17].

Table 2 Summary of guideline recommendations for sulfonylurea use in patients with diabetes, with particular focus on gliclazide

	Second-line treatment recommendation in patients with suboptimal glucose control on metformin	Guideline information specific to gliclazide MR
2015 UK (NICE/SIGN) guidelines [32]	DPP4i, pioglitazone or an SU	NA
Canada guidelines – 2020 Update [34]	GLP1-RA, SGLT2i, DPP4i, SU, acarbose, TZD	Gliclazide preferred over glyburide owing to the lower risk of hypoglycaemia
2020 Australian guidelines [33]	SGLT2i, DPP4i, SU, GLP-1RA	Gliclazide associated with fewer hypoglycaemia episodes versus other SUs Gliclazide (unlike other SUs) does not increase the risk of weight gain compared with metformin
2021 American Diabetes Association guidelines [123]	Minimise hypoglycaemia: DPP4i, GLP-1RA, SGLT2i, TZD Minimise weight gain: GLP-1 RA, SGLT2i Minimise cost: SU, TZD	NA

DDP4i dipeptidyl peptidase 4 inhibitor, *GLP1-RA* glucagon-like peptide-1 receptor agonists, *MR* modified release, *NA* not applicable, *NICE* National Institute for Health and Care Excellence, *SGLT2i* sodium–glucose co-transporter-2 inhibitors, *SIGN* Scottish Intercollegiate Guidelines Network, *SU* sulfonylureas, *TZD* thiazolidinediones, *UK* United Kingdom

A recent study showed that, within the UAE, only 39% of Emirati with diabetes and 37% of non-Emirati with the disorder had a mean glycated haemoglobin (HbA_{1c}) level of < 7% (the target level), highlighting that many patients do not have good glycaemic control and are at risk of developing complications [18]. Although patients aged < 20 years represented a smaller proportion of the diabetic population, 53% of these individuals in this age group had an HbA_{1c} of > 9%, and only 9% had an HbA_{1c} of < 7% [18]. In patients with high-risk T2D, complications are common and lipid control is often suboptimal, further increasing the patient's cardiovascular risk [19]. Data from 2012 to 2016 showed that the majority of patients who had high-risk diabetes had an HbA_{1c} of > 8% [19]. Given the chronic, progressive nature of the condition, it is imperative that high-risk patients and those of younger age receive additional support to improve their glycaemic control.

The proportion of patients who had an elevated HbA_{1c} level was found to have changed very little between 2012 and 2016 (from 65% to 61%), indicating that, despite advances in medical interventions, the proportion of patients achieving glycaemic control does not appear to have improved and only a proportion of patients are achieving their glycaemic targets [18].

Impact of Early Glycemic Control on Long-Term Diabetes Management and Complications

It is well established that there is an association between increasing HbA_{1c} levels and an increasing risk of developing diabetes complications, including retinopathy, severe non-proliferative/proliferative retinopathy, clinical neuropathy and microalbuminuria [20–22]. An HbA_{1c} of ≥ 10% was associated with a 4.42-fold greater risk of developing end-stage renal

disease (ESRD), and a 1-point increase in HbA_{1c} was found to significantly increase the risk of developing diabetic retinopathy [odds ratio (OR), 4.53; 95% confidence interval (CI) 2.11–9.72; $P < 0.001$] [23, 24]. A 1-point decrease in HbA_{1c} levels was also associated with a 37% decrease in microvascular risk ($P < 0.001$) [25].

Long-term cardiovascular complications also tend to be linked with higher HbA_{1c} levels. A recent meta-analysis showed that a 1% increase in HbA_{1c} was associated with an 18% increase in myocardial infarction (MI) in both men and women, irrespective of their age and diabetes status [26]. In another study, a 1-point increase in HbA_{1c} was associated with a 22% increase in the risk for the composite endpoint of all-cause mortality, MI and ischaemic stroke, after adjusting for baseline factors, such as age and sex [27].

The finding that elevated HbA_{1c} is associated with complications was supported by another study, which showed that HbA_{1c} outside the target range was the strongest predictor for all-cause mortality, acute MI, stroke and hospitalisation for heart failure (HF) among patients with T2D, with or without pre-existing conditions [28]. Similarly, a retrospective cohort study ($N = 47{,}161$) showed that, among patients with $HbA_{1c} \geq 7\%$, those who had therapy intensification delayed by 1 year had a significant increase in the risk of developing MI [hazard ratio (HR); 1.67; 95% CI 1.39–2.01; $P < 0.01$] and other cardiovascular events (HR, 1.62; 95% CI 1.46–1.80; $P < 0.01$) at 5 years compared with those who received immediate therapy intensification [29]. Therefore, establishing good glycaemic control early is essential to reduce the risk of diabetes-associated complications.

Early normalisation and long-term maintenance of blood glucose and HbA_{1c} values in patients with diabetes is a predictor of long-term control and outcomes, so early target achievement has what is known as a "legacy effect" on later outcomes. In the DISCOVER study, the single biggest predictor of having an HbA_{1c} level of $< 7\%$ after 3 years was an HbA_{1c} of $< 7\%$ at 6 months [30]. This finding was also demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS), which showed reductions in the relative risk of various outcomes achieved after 10 years of intensive therapy with insulin and SU compared with conventional therapy (Table 1) [31].

Guidelines and Real-Life Practice: SUs in the Management of Type-2 Diabetes

In addition to metformin, diabetes clinical practice guidelines generally agree that, in the absence of compelling indications, such as established CVD, diabetic kidney disease (DKD) or HF, the choice of second-line treatment should be dependent on the degree of glycaemia, the effectiveness of treatment, cost and safety profile [32–34].

Variations in safety profiles have been noted between SU agents, likely due to differences in binding affinities for SU receptors. Unlike certain other SU, gliclazide has a high affinity for the SUR1 receptor present on pancreatic β cells, but does not have a high affinity for the SUR2A and SUR2B receptors present on the heart and smooth muscle cells, respectively. It is speculated that this may be the reason for the differences in the rates of cardiovascular events and hypoglycaemia between SU agents [35].

As presented in Table 2, SUs are a common choice for second-line therapy according to evidence-based clinical practice guidelines [32–34]. Within both the Australian and Canadian guidelines, gliclazide is preferred as it has the lowest potential for hypoglycaemia, as well as data supporting the long-term renal benefits and a proven cardiovascular safety profile [33, 34]. Additionally, the Canadian guidelines describe the low cost of SUs compared with most other classes of treatment [34]. Consistent with these guidelines, data from a Japanese study suggest that SUs are more commonly used as part of combination therapy rather than monotherapy [36], particularly among patients with higher HbA_{1c} levels, lower body mass index (BMI) and longer duration of T2D [37]. According to a consensus statement from the American Diabetes Association (ADA) and European Association of the Study of Diabetes (EASD), which does not meet the criteria for

Table 3 Observational and randomised control studies assessing the risk of severe hypoglycaemia with gliclazide use

Trial	Type of study	Strategy	Comparator	*N* (SU)	Duration	Baseline HbA_{1c}	End-of-trial HbA_{1c}	Severe hypoglycaemia
DIA-RAMADAN [43]	Real-world observational	Gliclazide MR based	None	1244	3.5 months	7.5%	7.2%	0/100 person-years
UKCPRD [44]	Real-world observational	Gliclazide MR	Sitagliptin	1986 (993)	± 9 years	Gliclazide MR: 8.5% (7.8–9.7) Sitagliptin: 8.6 (7.8–9.8)	51% more likely to reach < 6.5%	0.12 versus 0.03 (0.1/100 person-years)
ADVANCE [45]	Intensive glucose control	Gliclazide MR based	SOC	11,140 (5571)	5.0 years	7.5%	6.5%	2.7% (intensive) 1.5% (standard)
STENO-2 [46]	Intensive glucose control	Metformin, gliclazide, insulin	SOC	160 (80)	3.8 years	8.4%	7.6%	2.5% (intensive) 3.75% (standard)
GUIDE [47]	RCT	Gliclazide MR	Glimepiride	845 (405)	6 months	8.4%	7.2%	0
Foley et al., 2009 [48]	RCT	Gliclazide	Vildagliptin	1092 (546)	2 years	8.7%	7.1%	0
Filozoft et al., 2010 [49]	RCT	Gliclazide & metformin	Vildagliptin & metformin	1007 (494)	1 year	Mean 8.5%	7.65%	0
STEADFAST [50]	RCT	Gliclazide	Vildagliptin	557 (278)	3 months	6.79%	6.76%	0

HbA_{1c} glycated haemoglobin, *MR* modified release, *RCT* randomised control trial, *SOC* standard of care, *SU* sulfonylurea

Table 4 Summary of cardiovascular safety findings from trials comparing various sulfonylurea agents

Study	Risk assessed	Treatment comparison	HR (95% CI)	*P* value
ADVANCE [45]	On-treatment macrovascular events	Gliclazide MR versus other SU	0.94 (0.84, 1.06)	0.32
ADVANCE ON [57]	Macrovascular events, after follow-up	Gliclazide MR versus standard glucose control	0.92 (0.85, 1.00)	0.06
CAROLINA [55]	3-point major adverse cardiovascular events risk	Non-inferiority of linagliptin versus glimepiride as add-on to metformin	0.98 (0.84, 1.14)	< 0.001 (for inferiority)
TOSCA-IT [56]	Composite of first occurrence of all-cause death, non-fatal MI, non-fatal stroke or urgent coronary re-vascularisation	Pioglitazone versus other SUs (glibenclamide, glimepiride, gliclazide)	0·96 (0.74, 1.26)	0.79

CI confidence interval, *HR* hazard ratio, *MI* myocardial infarction, *MR* modified release, *SU* sulfonylurea

trustworthy clinical practice guidelines [38], SUs are not favoured in the algorithms for T2D patients where there is established CVD and a compelling need to minimise weight gain or hypoglycaemia [39]. However, the risk of hypoglycaemia or weight gain appears to be lower, and the cardiovascular safety better, with later-generation SUs, which have favourable efficacy, safety and cost profiles.

The AGREE evidence rating system was developed for the purpose of evaluating the quality of published guidelines [40]. Different aspects of the guidelines are considered within the evaluation, including rating the scientific rigour of development and determining whether there is an explicit link between the recommendations and supporting evidence. Using this method, the National Institute for Health and Care Excellence (NICE) guidelines have a 97% rating, the Canadian guidelines an 83% rating and the Australian guidelines 76%, while the ADA consensus was given a 50% rating [41].

A consensus document which addresses the use of – and confirms the efficacy and safety of – newer-generation SUs was developed by experts in T2D management from the Gulf Cooperation Council (GCC) countries [42]. Unlike the ADA/EASD consensus, the GCC consensus was developed following an advisory board and extensive literature reviews and surveys within the Gulf region. Topics included epidemiology, long-term SU efficacy and safety, as well as information specific to Ramadan and weight gain. This consensus was endorsed by the Gulf Association of Endocrinology and Diabetes, the Bahrain Diabetes Society, the Emirates Diabetes and Endocrine Society, and the Saudi Scientific Diabetes Society and was informed by studies assessing the risks of hypoglycaemia, cardiovascular safety and renal benefits of the later-generation SU, gliclazide modified release (MR) [42].

The Risk of Hypoglycaemia with SU Therapy

While the goal of diabetic therapy is reducing HbA_{1c} levels, establishing a balance is necessary to avoid hypoglycaemia. Several studies have investigated the absolute rates of hypoglycaemia with SUs (Table 3) [43–50]. Within two cohort studies, the rate of hypoglycaemia with later-generation SUs, such as gliclazide modified release (MR), was low [43, 44], and in the UK Clinical Practice Research Datalink (CPRD) study specifically, patients were more likely to achieve an HbA_{1c} level of < 6.5% with gliclazide

MR than with sitagliptin [44], with similar low rates of hypoglycaemia. Across the four randomised controlled trials (RCTs) reviewed, there were no cases of severe hypoglycaemia.

As per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence rating system, which assesses information for inclusion within guidelines, RCTs are generally considered to have a higher quality rating than observational studies, as they usually have less bias; therefore, more emphasis is placed on their findings [51]. When compiled from a range of low-biased RCTs, meta-analyses generally have the highest impact rating [51, 52]. The RCT by Foley and colleagues [48] was included within a meta-analysis that comprised 219 RCTs that investigated 24 anti-diabetic agents in 121,914 patients with T2D [53]. The relative risk of hypoglycaemia was lowest with gliclazide compared with all other SUs (3.6% for gliclazide, 8.9% for glimepiride, 10.2% for glyburide and 13.9% for glipizide). In fact, the relative risk of hypoglycaemia for gliclazide was similar to that of metformin [53]. Taken together, these findings suggest that the risk of developing severe hypoglycaemia is lowest for patients taking later-generation SU, such as gliclazide MR, and in particular the absolute risk of hypoglycaemia is very low.

Cardiovascular safety

People with T2D are at increased risk of cardiovascular complications compared with those without diabetes, with a 53% increased risk of unstable angina, 54% increase in MI risk, 56% increase in HF risk and 72% increase in stroke risk [2].

In a cohort study comparing adverse cardiovascular events between different SU agents, second-generation, long-acting SUs (e.g. gliclazide MR and glimepiride) are not associated with an increased cardiovascular risk compared with older-generation SUs (e.g. glyburide, glipizide and tolbutamide) [54]. Similar results were reported in other studies (Table 4) [45, 55–57]. The ADVANCE trial [45] and the ADVANCE ON extension [57] demonstrated that tight glycaemic control ($HbA_{1c} < 6.5\%$) could be achieved and maintained for approximately 5 years using an SU-based regimen without increasing the risk of cardiovascular events. Glimepiride, a second-generation SU, was non-inferior to the dipeptidyl peptidase 4 inhibitor linagliptin with regard to cardiovascular risk [55], and the risk of major adverse cardiovascular events was similar with pioglitazone versus other SUs in the TOSCA-IT study [56].

In a retrospective study based on the Danish nationwide registry of 107,806 participants with T2D, compared with metformin, the SUs glimepiride, glibenclamide and tolbutamide were all associated with an increase in cardiovascular risk, as measured over a 9-year period [58]. Comparatively, gliclazide and repaglinide were the only agents to not be associated with an increased cardiovascular risk [58]. A meta-analysis by Simpson and colleagues, which included 18 studies and 167,327 patients, showed that gliclazide was associated with a lower all-cause mortality rate and a lower risk of cardiovascular-related mortality compared with other SUs [59].

Renal Benefits

Given that diabetic nephropathy is a leading cause of chronic kidney disease (CKD) and ESRD, ensuring anti-diabetic therapy does not have a deleterious effect on kidney health, but rather benefits, is important [60]. In the ADVANCE study, gliclazide-based intensive glucose control resulted in a significant reduction in the incidence of major microvascular events compared with standard therapy [45]. Similar results were reported in the follow-up studies – ADVANCE (2) and ADVANCE ON [57, 61]. Intensive glucose control provided a 9% reduction in microalbuminuria risk, a 65% reduction in the risk of ESRD after 5-year follow-up in ADVANCE (2) [61] and a 21% reduction in risk of worsening nephropathy after 5.9-year follow-up in ADVANCE ON [57] (Table 5).

In a review of the relative renal risk across different SU therapies in patients with DKD, glimepiride was suggested as appropriate for patients with an estimated glomerular filtration rate (eGFR) of > 60 mL/min/1.73 m^2, but is

Table 5 Summary of renal safety findings from trials assessing gliclazide therapy

Study	Treatment comparison	Risk assessed	HR (95% CI)	*P* value
ADVANCE [45]	Gliclazide MR-based (intensive blood glucose control) or standard glucose control with other SU	Major microvascular events	0.86 (0.77, 0.97)	0.01
		Worsening nephropathy	0.79 (0.66, 0.93)	0.0006
ADVANCE [61]	Gliclazide MR-based (intensive or standard glucose control) and perindopril/indapamide or matching placebo	ESRD risk	0.35 (0.15, 0.83)	0.01
		New-onset microalbuminuria	0.91 (0.85, 0.98)	0.01
ADVANCE ON [57]	Gliclazide MR-based (intensive blood glucose control) or standard glucose control with perindopril/indapamide or matching placebo	ESRD risk	0.85 (0.45, 1.62)	0.01

CI confidence interval, *HR* hazard ratio, *ESRD* end-stage renal disease, *MR* modified release, *SU* sulfonylurea

considered unsafe in patients with an eGFR $\leq$ 30 mL/min/1.73 m^2 [62]. The use of glibenclamide in patients with an eGFR of 60–90 mL/min/1.73 m^2 should be limited as it is contraindicated for patients in stage $\geq$ 3 CKD. Comparatively, gliclazide was suggested as being appropriate for patients with an eGFR of > 30 mL/min/1.73 m^2 [62]. It is worth noting that glimepiride, glibenclamide and gliclazide are all contraindicated in patients with severe renal dysfunction, and no specific eGFR rates are suggested for dose adjustment [62].

Hypoglycaemia and Ramadan

The risk of hypoglycaemia is of particular concern in patients with T2D who fast during the month of Ramadan. Two studies have demonstrated that the rates of symptomatic hypoglycaemia in the fasting patients were similarly low with gliclazide MR or sitagliptin, with higher rates of hypoglycaemia observed with other SU therapies (Table 6) [63, 64]. In the DIA-RAMADAN study, all patients received gliclazide MR as monotherapy or in combination with any other diabetes treatment except insulin, and the rates of symptomatic hypoglycaemia remained low and no severe hypoglycaemia was reported over 14–18 weeks [43]. These findings support the use of gliclazide over other SU therapies in Muslim patients with diabetes fasting during Ramadan.

Weight Changes with Gliclazide Treatment

Contrary to the ADA/EASD consensus [39], body weight did not appear to change substantially with gliclazide therapy [43, 45, 65]. Patients receiving gliclazide MR with a baseline BMI of $\geq$ 25 kg/m^2 lost 0.9–2.2 kg in the EASY-Dia study [65]. In the DIA RAMADAN study, the average weight loss in the overall study population was 0.5 kg [43], but was highest (0.7 kg)

Table 6 Comparative rates of symptomatic hypoglycaemia across Ramadan-specific studies according to sulfonylurea therapy

Study	Population, *n*	Countries included	Symptomatic hypoglycaemia (% of patients)
Al Sifri et al., 2011 [63]	1066	Middle Eastern countries	Gliclazide (6.6%) Glimepiridine (12.4%) Glibenclamide (19.7%) versus sitagliptin (6.7%)
Aravind et al., 2012 [64]	870	India, Malaysia	Gliclazide (1.8%) Glibenclamide (5.2%) Glimepiridine (9.1%) versus sitagliptin (3.8%)
DIA-RAMADAN [43]	1244	Middle East, India, South-East Asian countries	$\geq$ 1 symptomatic hypoglycaemic event: Gliclazide during Ramadan (2.2%)

in patients residing in the Middle East [66]. In the ADVANCE trial, an average gain of only 0.1 kg was reported after 5 years of intensive glucose control with gliclazide MR [45]. These findings suggest that gliclazide treatment does not negatively impact patients' weight.

Impact of COVID-19 infection

While long-term data on the impact of coronavirus disease 2019 (COVID-19) infection in patients with diabetes have not yet been reported, it is apparent that these patients are at a distinct disadvantage compared with individuals who do not have diabetes if they contract the virus. Adjusted, matched hazard ratios (HRs) show that, compared with patients with well-controlled glycaemia, patients with diabetes with poorly controlled glycaemia in China experience an 86% increase in mortality, a 53% increase in acute respiratory distress syndrome, an 88% increase in acute kidney injury, a 76% increase in acute heart injury, as well as an increased rate of disease progression [67]. The combination of hyperglycaemia and COVID-19 has a significant effect in patients with diabetes, with increased medical interventions being required [67]. Similarly, a single-centre, retrospective study from Saudi Arabia that assessed medical records of hospitalised patients with COVID-19 (n = 439) found that those with diabetes (n = 300) had a significantly higher death rate (20.5% versus 12.3%; P = 0.04) and lower survival time (P = 0.016) than those without diabetes, although other factors such as age, HF and smoking were more significant predictors of fatal outcome. Random blood glucose level $\geq$ 11.1 mmol/L was significantly associated with intensive care admission [68].

HYPERTENSION IN THE GULF REGION

Blood Pressure Control and Guidelines

The prevalence of hypertension (BP $\geq$ 140/90 mmHg) in the UAE was 31% in a meta-analysis of 15 cross-sectional studies conducted between 1995 and 2020 (total 139,907 participants), whereas awareness was low (29%) and 38% had controlled BP [69]. More broadly, the prevalence in the Middle East was approximately 33% in a 2017 study of 10,516 participants, in which awareness was 49% and only 19% had their BP adequately controlled [70]. In contrast, the prevalence of hypertension in 12

high-income countries (including Australia, Canada, Finland, Germany, Ireland, Italy, Japan, New Zealand, South Korea, Spain, the UK and the USA) was estimated at 33–52% in women and from 34–59% in men, with awareness and treatment rates ranging from 40% to 80% across age groups [71]. The lifetime risk of developing hypertension increases with advancing age, regardless of ethnicity, with people having on average an 80% chance of developing hypertension by 80 years of age [72].

Hypertension is a major risk factor for CVD mortality and morbidity. In a study of 600 patients with hypertension, 91% had at least one additional risk factor that increased the likelihood of developing CVD [1]. One such risk factor is diabetes, and in a study of > 15,000 patients with T2D who had recently been diagnosed with hypertension, an unchecked BP within 1 year of diagnosis was shown to increase the risk of a cardiovascular event by > 30% over the course of 3 years [73].

In a meta-analysis of 61 observational studies that included 1 million adults (aged 40–89 years; BP > 115/75 mmHg), the relative risk of death from ischaemic heart disease (IHD) and other vascular causes doubled with each incremental rise in BP [74], so for example, there would be a one-fold increase in this risk at 115/75 mmHg, two-fold at 135/85 mmHg, four-fold at 155/95 mmHg and eight-fold at 175/105 mmHg. The risk of mortality from IHD was correlated with increasing systolic BP (SBP) in patients aged ≥ 40 years; therefore, a reduction in mean SBP of 2 mmHg would result in a 7% reduction in the risk of IHD mortality and a 10% reduction in the risk of stroke mortality. Further, across the age groups assessed from 50 years of age, a linear relationship was found between increasing BP [both SBP and diastolic blood pressure (DBP)] and an increasing risk of stroke mortality [74].

In another meta-analysis of 40 randomised controlled trials and 100,354 patients with T2D, each 10-mmHg reduction in SBP significantly improved macro- and microvascular outcomes (Fig. 1) [75]. Therefore, reducing and controlling BP in patients with hypertension is critical to reduce the risk of arterial heart disease. The reasons for the high proportion of patients with resistant hypertension are varied, but include adherence problems, treatment doses that are too low, an absence of synergy between the treatments used, and clinical inertia [76].

Blood Pressure Control and Clinical Inertia

Clinical inertia, characterised by a physician's reluctance to initiate or intensify therapy when a patient has not reached the therapeutic goals, is considered to be a major cause of uncontrolled hypertension [77]. An anonymised European survey of 2629 physicians showed that physicians significantly underestimated the number of patients not achieving their BP targets, and 22.5% of general practitioners specifically considered the target BP (140/90 mmHg) to be too tight or unachievable [78]. A study by Ali and colleagues determined that 87% of patients in primary care experienced therapeutic inertia [79]. In that study, the most common reason for no action being taken was that the physician did not believe the BP reading was accurate and intended to review it at the next visit [79].

Given the fluctuations in BP measurements seen in an individual patient, determining the ideal BP target can be complicated [80]. For example, a study assessing individuals without atherosclerotic CVD showed that those with the lowest incidence of coronary artery calcium and diffuse coronary artery calcium had an SBP of 90–99 mmHg [81], suggesting that a target SBP of < 100 mmHg may be appropriate for some. However, this is an unrealistic target for the average patient, so a few different methods of categorising BP have been developed, with minor variations in the target BP ranges. The ambulatory BP and the home BP monitoring systems tend to be more frequently used than office BP, as they have slightly higher tolerances and are more easily reproducible [82].

In the healthcare setting, a patient's BP should be measured when they are seated comfortably and they should not have smoked recently or exercised within the last half an hour. The cuff should be placed directly on the patient's upper arm, and the average of the

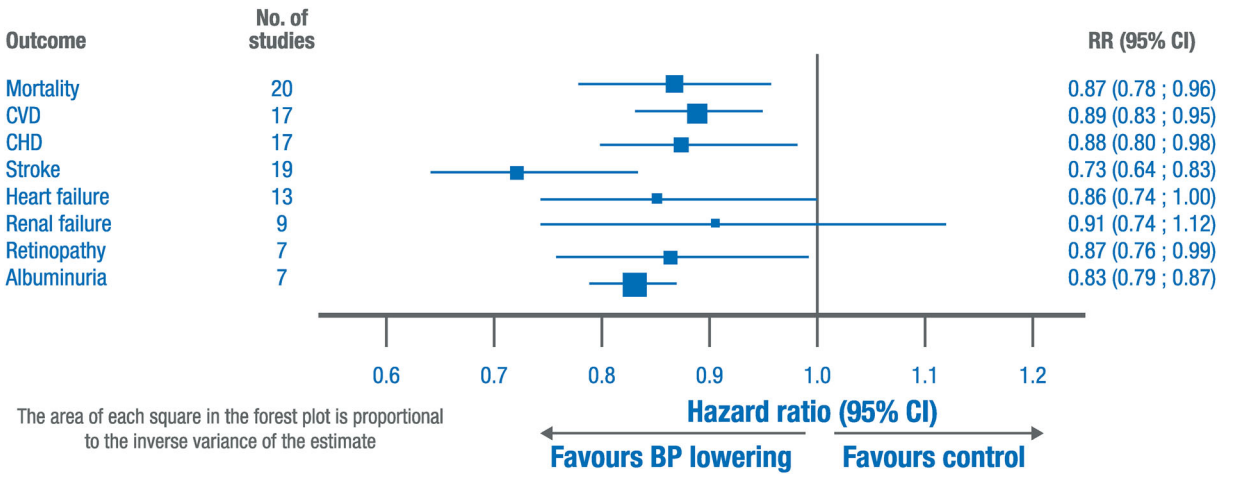

Fig. 1 Changes in all-cause mortality, macrovascular and microvascular outcomes following a 10-mmHg reduction in systolic blood pressure in patients with type 2 diabetes. Adapted with permission from *JAMA*. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis.;313(6):603–15 [75]. Copyright © 2015 American Medical Association. All rights reserved. *BP* blood pressure, *CHD* coronary heart disease, *CI* confidence interval, *CVD* cardiovascular disease, *RR* risk ratio

second and third readings should determine the patient's BP [82]. Home BP monitoring kits are a valuable and recommended tool that will not only promote patient involvement, but also provide a comparison between at-home resting BP and what is seen in-clinic (i.e. office BP), which may assist physicians in determining whether the office BP is accurate [83]. Suggested as a routine, daily activity, home BP monitoring is especially valuable for Muslim patients who may not be able to expose their bare arm for a BP cuff during their clinic visit.

While lifestyle changes are important for the management of hypertension, considerable improvements in BP can be seen with medication. However, physicians can be reluctant to add another class of medication to a patient's regimen if they are not reaching their target owing to the perceived risk of hypotension. According to the 2015 guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the management of hypertension, the 'Rule of 10' demonstrates that doubling the dose of any one medication will generally result in only a 2 mmHg decrease in SBP, whereas the addition of a second medication can result in a 10 mmHg reduction in BP [84]. In clinical practice, physicians can apply the 'Rule of 10' to determine the number of medications needed to reach target BP, i.e. by calculating the difference between the current and target BP and dividing this difference by 10 to determine the approximate number of medications needed to achieve the patient's target BP.

Single-pill combinations (SPCs) of anti-hypertensive medications could improve patient outcomes. When compared with free pill combinations, SPCs reduce the 1-year risk of any cardiovascular event by 21% and can reduce the risk of ischaemic heart disease by 39%, as determined by a population-based cohort study of > 5 million individuals [85]. Initial treatment with an SPC also provides better, more rapid BP control than free pill combinations, taking patients 28% less time to achieve the targeted BP within the first year of treatment [86]. In an open-label RCT conducted over 6 months, a higher proportion of patients on an SPC containing perindopril, indapamide and amlodipine achieved the BP target compared with those who received the same therapy as individual pills (85% versus 53%, $P < 0.05$), and adherence rates were higher in the patients taking the SPC (87% versus 61%, $P < 0.05$) [87].

Closing the Gap between Guidelines and Clinical Practice in Hypertension

To improve BP management and reduce the risk of cardiovascular events associated with hypertension, most international guidelines agree on a stepwise approach, which involves the escalation of therapy and the use of SPCs, when possible (Table 7) [82, 88–90]. The use of the ACEis/ARBs and CCBs as first-line treatment is a common recommendation throughout the guidelines; however, both the NICE and the British Hypertension Society guidelines recommend that patients aged > 55 years or those of African or Caribbean descent start therapy with a CCB specifically [88, 90]. Additionally, the NICE guidelines suggest that, before escalating therapy by increasing the dose or adding another medication, physicians should discuss the treatment plan with the patient and check that the patient is adhering to the previous regimen [90].

Management of Hypertensive Patients with Cardiovascular Risk Factors

As hypertension significantly increases the risk of CVD, risk assessments should be conducted in certain patient groups on a regular basis [91]. The NICE guidelines recommend that a CVD risk assessment should be offered to adults aged over 40 years using tools such as the QRISK2 (or later versions), which assist in the identification of patients who are at a high risk of developing CVD [92]. The QRISK2 risk assessment may even be conducted with healthcare data on file; it is not required in patients already identified at high risk of CVD, such as those with established CVD, or familial hypocholesterolaemia, T2D or CKD stage 3–5 [92]. These assessments can predict a patient's lifetime risk of developing CVD and highlight the benefit of lifestyle modifications [91]. Patients with a ≥ 10% risk of developing CVD within 10 years should be offered atorvastatin 20 mg [92]. In addition, this group should be offered anti-hypertensive therapy if they have stage 1 hypertension and BP > 140/90 mmHg. These patients should also have electrocardiogram (ECG), renal and ophthalmic assessments; monitoring the health of organs (including the kidneys and heart) in patients with hypertension is recommended as a means to prevent organ damage and monitor cardiovascular risk [93].

Intensive anti-hypertensive therapy involves treating patients with the intention of reaching a BP that is lower than standard targets. Despite significant improvements in BP management and reductions in cardiovascular risk seen with this method, it is not commonplace in routine clinical practice. A study by Zhang and colleagues, of patients aged > 60–80 years in China, showed that the intensive therapy aiming for a BP target of 110–130 mmHg compared with 130–150 mmHg resulted in a reduction in the risk of the composite primary endpoint of stroke, acute coronary syndrome, acute decompensated HF, coronary re-vascularisation, atrial fibrillation or cardiovascular death compared with those in the standard therapy arm (HR 0.74; 95% CI 0.60–0.92; $P = 0.007$) [94]. Except for hypotension, which was more common in the intensive therapy arm than the standard treatment arm (3.4% versus 2.6% of patients; relative risk 1.31; 95% CI 1.02–1.68; $P = 0.03$), the incidences of treatment-related dizziness and syncope, and of treatment-related renal outcomes (e.g. eGFR reduction or elevation in serum creatinine levels), were not significantly different between treatment arms [94].

Evidence with RAASis on Morbidity and Mortality Reduction

Although the guidelines agree that first-line therapy for most patients with hypertension should include an ACEi or ARB, determining which specific RAASi to use can be challenging [82, 83, 88]. According to the International Society of Hypertension's 2020 guideline, an ideal treatment should be evidence-based in relation to its ability to prevent morbidity and mortality [82].

Multiple meta-analyses have evaluated the effect of ACEi and ARB on cardiovascular outcomes (Table 8). Across these studies, ACEis showed improved outcomes compared with

Table 7 International guideline recommendations for the management of hypertension

	Recommends single-pill combinations	General recommendations	Recommendations specific to the guideline
2020 ISH guidelines [82]	Yes	1. Low-dose ACEi/ARB + DHP-CCB 2. Increase ACEi/ARB + DHP-CCB to full dose 3. Add thiazide/thiazide-like diuretic 4. Add spironolactone or, if contraindicated or not tolerated, amiloride, doxazosin, epilerenone, clonidine or beta-blocker	Specific guidance provided for Black patients, ACEi not recommended in the first instance, instead recommend a low-dose ARB and thiazide/thiazide-like diuretic. For step 3, add diuretic/or ACEi/ARB
BHS Guidelines 2004 [88]	Yes	1. If < 55 years of age and not Black: ACEi/ARB or beta-blocker 2. Add a CCB or a diuretic (thiazide/thiazide-like) 3. Add a diuretic 4. Add (thiazide/thiazide-like) or spironolactone/other diuretic	If > 55 years of age or Black for step 1: CCB or diuretic (thiazide/thiazide-like diuretic)
2018 ESC/ESH guidelines [89]	Yes	1. ACEi or ARB + CCB or diuretic 2. ACEi or ARB + CCB + diuretic 3. Add spironolactone or other diuretic, alpha-blocker or beta-blocker	Consider monotherapy in low-risk grade 1 hypertension or frail patients Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation or younger women with, or planning, pregnancy
NICE hypertension guidelines 2019 [90]	Not mentioned	1. ACEi/ARB if < 55 years of age/with T2D 2. Add CCB/thiazide-like diuretic 3. Add either CCB or thiazide-like diuretic 4. Add a fourth anti-hypertensive medication	If > 55 years of age/Black African or African–Caribbean ethnicity consider ARB instead of ACEi If > 55 years of age and have no T2D or are of African or Caribbean ethnicity, offer a CCB ACEi and ARB should not be used in patients who are pregnant/breastfeeding or in those planning pregnancy unless absolutely necessary

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BHS* British Hypertension Society, *CCB* calcium channel blocker, *DHP* dihydropyridine, *ESC* European Society of Cardiology, *ESH* European Society of Hypertension, *ISH* International Society of Hypertension, *MI* myocardial infarction, *NICE* National Institute for Health and Care Excellence, *T2D* type 2 diabetes

placebo and active comparators, including ARBs [7, 95, 96]. In particular, a meta-analysis by van Vark and colleagues reported a 10% reduction in the risk of all-cause mortality, attributed exclusively to the ACEi class, and of the ACEi trials in the analysis, those that studied perindopril reported the largest improvements in mortality risk [7].

While both ACEis and ARBs act on angiotensin (Ang) II to reduce vascular resistance and aldosterone release, ACEis block the synthesis of Ang II, whereas ARBs prevent Ang II from binding to its AT1 receptor [95]. Among other activities, ACEis increase bradykinin bioavailability and nitric oxide levels, promoting vasodilation. Comparatively, ARBs have been associated with vasoconstriction [95]. These different mechanisms of action may explain the improved cardiovascular outcomes seen with ACEis compared with ARBs.

Certain factors, such as plasminogen activator inhibitor (PAI) and fibrinogen, are increased in patients with hypertension, leading to an increased risk of thrombus formation [97]. Therefore, reducing these factors in addition to reducing BP in patients with hypertension would assist in preventing cardiovascular events, particularly as a hypercoagulative state is more apparent in hypertensive patients [97]. In a study of 85 patients with hypertension and T2D, a 10-ng/mL reduction in PAI-1 was seen in patients on perindopril, but no reduction was seen with losartan over 12 weeks [98]. In another study in 28 patients with hypertension, both perindopril and losartan significantly reduced fibrinogen over 6 weeks compared with the control group [99].

By increasing bradykinin-induced tissue-type plasminogen activator (t-PA) release, ACEis favourably alter the fibrinolytic balance, which results in increased vasodilation and a reduced risk of CVD. In an RCT of 45 patients with hypertension, both perindopril and losartan increased tPA levels; however, this response was significantly greater with perindopril than with losartan (net tPA release ~500 versus ~250 ng/min, respectively) [100].

The relative risk of acute MI was assessed across various studies with different RAASi therapies in different patient populations (Fig. 2) [101]. Only two studies showed a reduction in the risk of this exploratory endpoint: the HOPE study, which demonstrated a risk reduction of 20% with ramipril versus placebo [102], and the EUROPA study, which showed a 22% risk reduction with perindopril versus placebo [103]. The studies with ARBs showed no significant impact on, or an increase in, the risk of MI [101].

In patients with hypertension who have not achieved adequate BP control, the addition of a CCB or a diuretic may be beneficial (Table 7). The STRONG study in patients with newly diagnosed or uncontrolled hypertension ($N = 1250$) showed that perindopril/amlodipine SPC recipients had a significant reduction from baseline in SBP of 41.9 mmHg and in DBP of 23.2 mmHg (both $P < 0.0001$ versus baseline) [104].

Several studies have investigated the impact of combination anti-hypertensive therapy on cardiovascular outcomes (Table 9) [104–108]. The PROGRESS study in patients with a history of stroke or transient ischaemic attack reported improvements in cardiovascular risk following treatment with perindopril (with or without amlodipine) compared with placebo [105]. In the ASCOT trial investigating lipid management in patients with hypertension, atorvastatin plus amlodipine/perindopril was associated with a lower relative risk for the primary endpoint of non-fatal MI or fatal coronary heart disease (CHD) compared with atorvastatin plus atenolol-based treatment [108]. Combination therapy with amlodipine (with or without perindopril) also showed improvements across various outcomes, including non-fatal and fatal MI or stroke, cardiovascular mortality and all-cause mortality compared with atenolol (with or without bendroflumethiazide) [107]. Finally, the ADVANCE trial showed that patients with T2D treated with perindopril plus indapamide had a significantly greater reduction in the risk of cardiovascular death and all-cause death than those who received placebo, although the risk of macrovascular events (i.e. cardiovascular death, non-fatal stroke or non-fatal MI) was not significantly reduced with perindopril plus indapamide [109]. Among patients in the perindopril plus indapamide group in the

Table 8 Meta-analyses comparing the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular outcomes and mortality in patients with hypertension

Study	Patient condition	Treatment	Number of trials	*N*	Effect on CVD and other outcomes
van Vark et al. 2012 [7]	~ 67% with hypertension	ACEi, ARB, non-ARB comparator	20	158,998	12% reduction in CVD deaths with ACEi and 4% reduction in CVD deaths with ARB
Strauss et al. 2006 [95]	–	ACEi versus placebo	23	68,631	Global death: OR 0.88 (95% CI 0.84–0.92; $P < 0.00001$)
					CV death: OR 0.84 (95% CI 0.76–0.92; $P = 0.0001$)
					Stroke: OR 0.83 (95% CI 0.71–0.98; $P = 0.08$)
					MI: OR 0.83 (95% CI 0.71–0.98; $P = 0.03$)
		ACEi versus all active comparators including ARB	–	150,943	Global death: OR 0.91 (95% CI 0.86–0.95; $P < 0.0001$)
					CV death: OR 0.88 (95% CI 0.82–0.95; $P < 0.0005$)
					Stroke: OR 0.94 (95% CI 0.83–1.06; $P = 0.31$)
					MI: OR 0.86 (95% CI 0.82–0.90; $P < 0.00001$)
Savarese et al. 2013 [96]	Without HF	ACEi versus placebo	26	53,791	Composite of CV death, MI or stroke: OR 0.83 (95% CI 0.744–0.927; $P = 0.001$)
					MI: OR 0.811 (95% CI 0.748–0.879; $P < 0.001$)
					Stroke: OR 0.796 (95% CI 0.682–0.92; $P < 0.004$)
					All-cause death: OR 0.908 (95% CI 0.845–0.975; $P = 0.008$)
					New-onset HF: OR 0.789 (95% CI 0.686–0.908; $P = 0.001$)
					New-onset DM: OR 0.851 (95% CI 0.749–0.965; $P = 0.012$)
		ARB versus placebo		54,421	Composite of CV death, MI or stroke: OR 0.920 (95% CI 0.869–0.975; $P = 0.005$)
					MI: OR 0.903 (95% CI 0.803–1.015; $P = 0.086$)
					Stroke: OR 0.900 (95% CI 0.830–0.977; $P = 0.011$)
					All-cause death: OR 1.006 (95% CI 0.941–1.075; $P = 0.866$)
					New-onset HF: OR 0.892 (95% CI 0.761–1.046; $P = 0.159$)
					New-onset DM: OR 0.855 (95% CI 0.798–0.915; $P = 0.001$)

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CI* confidence interval, *CV* cardiovascular, *CVD* cardiovascular disease, *DM* diabetes mellitus, *HF* heart failure, *MI* myocardial infarction, *OR* odds ratio

ADVANCE trial, those who received CCB therapy at baseline showed trends (although not significant) for greater reductions in the risk of major cardiovascular events and cardiovascular mortality compared with those not receiving CCBs, as well as a significant reduction in the

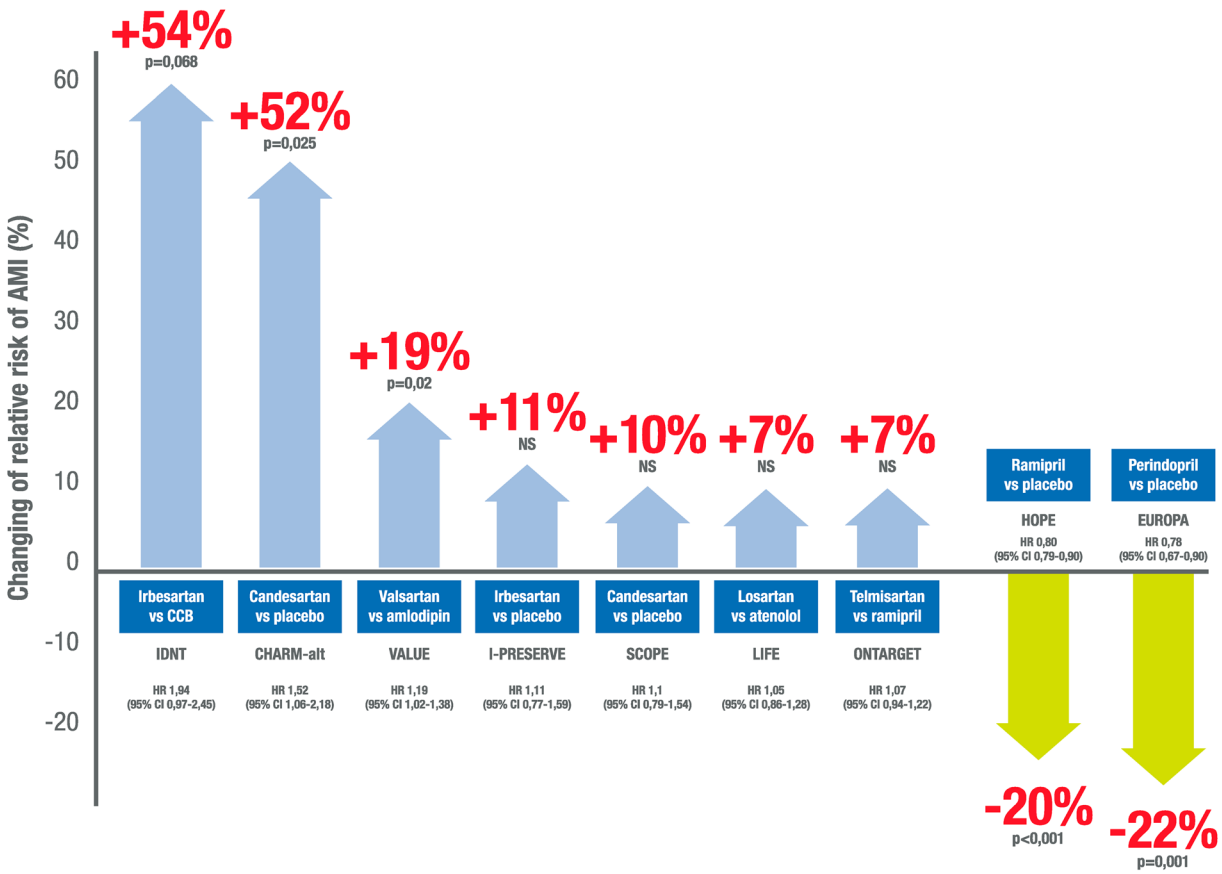

Fig. 2 The effects of different angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction compared with placebo or active comparator across different studies. Reprinted with permission from Springer: *Am J Cardiovasc Drugs*. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on prothrombotic processes and myocardial infarction risk. Dézsi CA, Szentes V. Am J Cardiovasc Drugs. 2016;16:399–406 [101]. Copyright © 2016. *AMI* acute myocardial infarction, *CCB* calcium channel blocker, *CI* confidence interval, *HR* hazard ratio

relative risk of all-cause mortality [106]. It is possible that the beneficial effects of the ACEi on endothelial function combined with the anti-atherosclerotic properties of the CCB may explain the improvements seen when these anti-hypertensive medications are combined [110].

Treatment with an SPC provides better adherence to treatment compared with the free combination of the same medications, as demonstrated by Koval and colleagues, who showed that 87% of high-risk patients with hypertension taking an SPC of perindopril, indapamide and amlodipine were adherent over 6 months compared with 61% of those taking the same regimen as individual pills [87]. Toth and colleagues also found that treatment with an SPC of perindopril/indapamide plus amlodipine in high-risk patients was beneficial, with mean (± standard deviation) changes in office SBP/DBP of −18.7 (± 8.3)/9.7 (± 7.2) mmHg for grade 1 hypertension, −30.4 (± 10.1)/14.7 (± 8.6) mmHg for grade 2, and −45.4 (± 15.1)/20.7 (± 12.1) mmHg for grade 3 hypertension (all $P < 0.0001$) [111]. Measured across 4 months in patients with high-risk hypertension, 72% of participants reached the target BP with the triple-drug combination of perindopril/indapamide plus amlodipine [111].

Table 9 Studies comparing the effect that combinations of anti-hypertensive medications have on cardiovascular and other health outcomes for patients with hypertension

Study	Patient condition	Duration	Therapy	*N*	Effect on CVD and other outcomes
PROGRESS [105]	Previous stroke/transient ischaemic attack	4 years	Perindopril (± indapamide) versus placebo	6105	Stroke: RRR 28% (95% CI 17–38%)
					Total coronary events: RRR 21% (95% CI 6–33%)
					Congestive HF: RRR 26% (95% CI 5–42%)
					Major vascular events: RRR 26% (95% CI 16–34%)
ASCOT [108]	Hypertension and at least three other CV risk factors	3.3 years	Atorvastatin and amlodipine (± perindopril) versus placebo	5138	CHD: HR 0.47 (95% CI 0.32–0.69; $P < 0.0001$)
			Atorvastatin and atenolol (± bendroflumethiazide and potassium) versus placebo	5167	CHD: HR 0.84 (95% CI 0.60–1.17; P = NS)
ASCOT-BPLA [107]	Hypertension and ≥ 3 other CV risk factors	5.5 years	Amlodipine (± perindopril) versus atenolol (± bendroflumethiazide and potassium)	19,257	Non-fatal MI and and fatal CHD: HR 0.90 (95% CI 0.79–1.05; P = NS)
					Non-fatal and fatal stroke: HR 0.77 (95% CI 0.66–0.89; $P = 0.003$)
					Total CV events: HR 0.84 (95% CI 0.78–0.90; $P < 0.0001$)
					All-cause mortality: HR 0.89 (95% CI 0.81–0.99; $P = 0.0247$)

Table 9 continued

Study	Patient condition	Duration	Therapy	*N*	Effect on CVD and other outcomes
ADVANCE [106]	T2D	4.3 years	Perindopril/indapamide with CCB at baseline	3427	Major CV events: RRR 12% (95% CI −8%, 28%)
					CV death: RRR 24% (95% CI −2%, 43%)
					Death from any cause: RRR 28% (95% CI 10%, 43%)
			Perindopril/indapamide without CCB at baseline	7713	Major CV events: RRR 6% (95% CI −10%, 19%)
					CV death: RRR 14% (95% CI −8%, 32%)
					Death from any cause: RRR 5% (95% CI −12%, 20%)

[a]Comparing arms ± CCB, major CV event $P = 0.38$; CV death $P = 0.21$; total death $P = 0.20$

CCB calcium channel blocker, *CHD* coronary heart disease, *CI* confidence interval, *CV* cardiovascular, *CVD* cardiovascular disease, *HF* heart failure, *HR* hazard ratio, *MI* myocardial infarction, *NS* non-significant, *RRR* relative risk reduction, *SPC* single-pill combination, *T2D* type 2 diabetes

Optimising Physician–Patient Communication and Improving Patient Lifestyle and Education in Patients with Diabetes and Hypertension

Both hypertension and diabetes require careful long-term management, and physicians should encourage positive lifestyle modifications, such as increasing physical activity, cessation of smoking and improving diet, in addition to anti-diabetic or anti-hypertensive medications [32, 82, 88, 112].

Patients today tend to be more involved in their healthcare management, and a reciprocal relationship with mutual cooperation between the physician and patient is now important [113]. Interventions to promote better communication between physicians and patients have resulted in significant benefits. In a systematic review by Harrington and colleagues, these interventions led to improvements in patient satisfaction, as well as improvements in the patient's perception of control over their health, information recall, adherence to recommendations, consultation attendance and clinical outcomes [114]. Therefore, physicians are encouraged to more actively engage their patients and to customise their treatment plan on the basis of the individual patient's needs and values. Current patient management requires consideration of a healthcare professional's attitude and communication skills and an understanding that healthcare should focus on the individual patient as a whole instead of simply curing the disease [115].

The benefit of patient education was further highlighted in the Structured Hypertension Education (SHED) study [116]. Once-weekly hypertension-related education sessions were held for 4 weeks by dieticians and specialist nurses for patients with hypertension. At the end of the study, 60% of patients undergoing these education sessions had achieved their BP targets compared with only 20% of those in the control group. Patients in the intervention group were also receiving significantly fewer pills [116]. One of the main reasons for poor patient compliance is a lack of understanding of the risks associated with hypertension, and education measures may assist in improving this issue and, in turn, improve patient outcome [117].

In addition to improving physician–patient communication, other lifestyle modifications should be encouraged. For patients with hypertension, dietary changes, such as the Mediterranean diet or the Dietary Approaches to Stop Hypertension (DASH) diet, can lead to significant improvements in BP [118, 119]. Patients with hypertension ($n = 133$) on the DASH diet experienced a mean reduction in SBP of −11.4 mmHg and in DBP of −5.5 mmHg [118].

A reduction in salt (sodium) to 2300 mg/day for the general population (or ≤ 1500 mg/day for African Americans, older individuals and patients with CKD, hypertension or diabetes) is recommended by the American Society of Hypertension (ASH) [120]. In patients with hypertension ($N = 412$; with a baseline SBP/DBP of ≥ 150/ ≥ 90 mmHg), a combination of the DASH diet and sodium reductions led to a 20.8-mmHg reduction in SBP and a 7.9-mmHg reduction in DBP [121].

In contrast, potassium has beneficial effects on BP control and the ASH recommend increasing potassium intake to 4.7 mg/day in patients with hypertension [120]. In a meta-analysis of 16 studies of patients with hypertension, increased potassium intake resulted in an estimated change in SBP of −5.32 (95% CI −7.20, −3.43) mmHg and in DBP of −3.10 (95% CI −4.53, −1.66) mmHg [122].

CONCLUSION

For patients with T2D, early sustained glycaemic control is essential for the prevention of macrovascular and microvascular complications. Similarly, in patients with hypertension, BP reductions can prevent cardiovascular complications.

The glucose-lowering effects of the later-generation SUs are similar to those of older SUs, but these newer agents such as gliclazide MR have the advantages of a lower incidence of hypoglycaemia with no risk of cardiovascular events and proven renal benefits. Within the various clinical guidelines, including the GCC

consensus, gliclazide MR is recommended as one of the best options for second-line treatment after metformin in patients with no known cardiovascular and renal diseases.

For patients with hypertension, a stepwise approach should be used when starting antihypertensive medication, with either an ACEi or CCB, depending on age and presence of associated risk factors, suggested as a first-line treatment owing to the lower risk of adverse cardiovascular events. For combination treatment, SPCs have been shown to improve adherence, and CCBs and diuretics in combination with an ACEi can successfully lower BP in patients with severe hypertension.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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