Diabetes journals

RAAS blockers: Best taken at bedtime

Marc Evans
Consultant Physician, Llandough Hospital, Cardiff

Hypertension commonly occurs in conjunction with insulin resistance, while activation of the renin–angiotensin–aldosterone system (RAAS) contributes to increased hepatic glucose release and decreased insulin sensitivity. Furthermore, hyperglycaemia increases serum aldosterone levels. Consequently, in addition to its blood pressure (BP)-lowering effects, RAAS blockade might also serve as an effective strategy to control impaired glucose tolerance. This concept has been illustrated by large studies, in which RAAS-blocking therapy was associated with a reduction in new-onset type 2 diabetes (Gillespie et al, 2005; Putnam et al, 2012).

Various clinical trials have suggested that different dose timings may result in different BP-lowering therapeutic effects. This may be particularly relevant in the case of RAAS blockade, as this system is highly circadian and activates during night-time sleep (Portaluppi et al, 2012). There is also a wealth of data to suggest that nocturnal BP may be a particularly important mediator of cardiovascular risk (Hermida et al, 2012), while elevated nocturnal BP has also been identified as a predictor of new-onset diabetes (Hermida et al, 2016). Based on such considerations, the latest study by Hermida and colleagues (summarised alongside) is the first to prospectively investigate whether bedtime administration of the entire daily dose of one or more hypertension medications offers better protection against development of new-onset diabetes than morning therapy, and whether RAAS inhibition or blockade is superior to any other treatment strategy for achieving this objective.

This was a prospective, randomised, open-label, blinded-endpoint trial of 2012 hypertensive people without diabetes: 976 men and 1036 women, with an average age of 52.7±13.6 years. The participants were randomised to ingest their prescribed hypertension medications either upon awakening or at bedtime. Investigators blinded to the treatment scheme assessed the development of new-onset diabetes. During a 5.9-year median follow-up, 171 participants developed type 2 diabetes. Compared with the morning-treatment group, the bedtime group showed the following:

- Significantly lower sleep-time mean BP, greater sleep-time relative BP decline and an attenuated prevalence of non-dipping at the final evaluation.
- A significantly lower risk of new-onset diabetes after adjustment for fasting glucose level, waist circumference, asleep systolic BP, dipping classification and presence of chronic kidney disease (hazard ratio [HR], 0.43; event rate 4.8% vs 12.1%).
- Greater benefit in terms of new-onset diabetes risk with angiotensin receptor blockers (ARBs; HR, 0.39), angiotensin-converting enzyme inhibitors (ACEIs; HR, 0.31) and beta-blockers (HR, 0.35).

Thus, according to this unique study, in hypertensive people without diabetes, ingestion of the entire daily dose of one or more BP-lowering medications at bedtime, compared with ingestion upon waking, results in significantly improved asleep BP control and prevention of new-onset diabetes. Moreover, the safety of the bedtime- and morning-treatment regimens was similar, while RAAS antagonism with bedtime ACEI or ARB treatment was superior to any other treatment strategy for reducing the risk of new-onset diabetes. The results of this study have significant implications for routine practice and strategies to reduce the risk of incident diabetes, particularly in the context of NHS England's widely publicised objective of reducing the incidence of type 2 diabetes. ■

References on opposite page

Diabetologia

Effects of morning or bedtime intake of antihypertensives on BP control and new-onset diabetes

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this prospective, randomised, open-label, blinded-endpoint trial, the authors compared the effects of administering antihypertensive medication before bed or upon waking on blood pressure (BP) control and risk of new-onset diabetes.

2 A total of 2012 people with hypertension but not diabetes were enrolled and followed up for a median of 5.9 years.

3 Compared with participants who took their medication in the morning, the bedtime group had a significantly lower BP while asleep (systolic, 109.6 vs 114.4 mmHg; diastolic, 63.4 vs 66.3 mmHg) and were more likely to experience a nocturnal dip in BP (32% vs 52%).

4 They also had a significantly lower risk of new-onset diabetes (event rate, 4.8% vs 12.1%; adjusted hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.31–0.61).

5 New-onset diabetes risk did not differ between antihypertensive agents in the morning group; however, in the bedtime group, angiotensin receptor blockers (HR, 0.39; 95% CI, 0.22–0.69), angiotensin-converting enzyme inhibitors (HR, 0.31; 95% CI, 0.12–0.79) and beta-blockers (HR, 0.35; 95% CI, 0.14–0.85) were all associated with reduced risk.

6 Other antihypertensive classes were not significantly better when taken at bedtime.

Hermida RC, Ayala DE, Mojón A, Fernández JR (2016) Bedtime ingestion of hypertension medications reduces the risk of new-onset type 2 diabetes: a randomised controlled trial. *Diabetologia* **59**: 255–65

Diabetologia

Effects of HIIT in people with T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this small study of 23 people with T2D, the authors evaluated a 12-week course of high-intensity interval training (HIIT) as a potential therapy to improve cardiac structure and function, as well as to improve liver fat levels and glycaemic control.

2 Compared with controls (n=11) who did not perform the exercise, HIIT improved cardiac structure (left ventricular wall mass increased by 12 g compared with a decrease of 2 g), and systolic function (stroke volume increased by 11 mL vs a decrease of 4 mL).

3 The HIIT group also had a 39% relative reduction in liver fat levels and a reduction in HbA_{1c} of 3 mmol/mol (0.3%) compared with an increase of 2 mmol/mol (0.2%).

4 The authors conclude that HIIT is effective at reducing fat depots that have a role in the aetiology of T2D and improve cardiac function, although improvements in HbA_{1c} were modest. They recommended it as a potential therapy to improve cardiac risk in people with this condition.

Cassidy S, Thoma C, Hallsworth K et al (2016) High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia* **59**: 56–66

Diabetes Care

Stress, depression and CV outcomes in diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 These authors compared the relationships between stress, depressive symptoms and cardiovascular (CV) outcomes in 4090 people with diabetes and 17 913 without, in a large, multi-racial cohort from the US.

2 Elevated stress and/or depression were more common in the diabetes cohort (36.8% vs 29.5%; P<0.001).

3 In models adjusted for CV risk factors and sociodemographics, the effects of stress and/or depressive symptoms were non-significant in people without diabetes over 5 years' follow-up.

4 However, in people with diabetes, the presence of either stress or depression was significantly associated with stroke (hazard ratio [HR], 1.57; 95% confidence interval [CI], 1.05–2.33) and CV death (HR, 1.53; 95% CI, 1.08–2.17).

5 The presence of both sets of symptoms together increased the risk of CV death to an even greater extent (HR, 2.15; 95% CI, 1.33–3.47).

Cummings DM, Kirian K, Howard G et al (2016) Consequences of comorbidity of elevated stress and/or depressive symptoms and incident cardiovascular outcomes in diabetes: results from the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Diabetes Care* **39**: 101–9

Diabetes

HDL-cholesterol does not affect T2D risk

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 These authors assessed whether genetic variants associated with low HDL-cholesterol levels were associated with T2D risk in a cohort of 47 627 people, of whom 2587 developed T2D.

2 Unsurprisingly, HDL-reducing gene scores were associated with HDL reductions of around 13–20%, and low HDL levels were associated with T2D risk, (hazard ratio [HR], 4.82 per 1-mmol/L HDL reduction).

3 In theory, this should have led to an HR for T2D of 1.44–1.77 in people with low-HDL genotypes; however, perhaps surprisingly, neither the HDL gene score nor the number of HDL-reducing alleles was associated with T2D risk.

4 The authors conclude that lifelong low HDL levels owing to genetic variation are not associated with T2D risk in the general population. Thus, low HDL does not appear to cause T2D; rather, T2D causes low HDL.

5 Therefore, recently suggested strategies to increase HDL levels to reduce T2D risk are unlikely to work.

Haase CL, Tybjærg-Hansen A, Nordestgaard BG, Frikke-Schmidt R (2015) HDL cholesterol and risk of type 2 diabetes: a Mendelian randomization study. *Diabetes* **64**: 3328–33

> ***"The authors conclude that lifelong low HDL-cholesterol levels owing to genetic variation are not associated with T2D risk in the general population. Thus, low HDL does not appear to cause T2D; rather, T2D causes low HDL."***

Diabetes Res Clin Pract

Statin use associated with higher HbA_{1c} in people with T1D

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 In this cross-sectional study of 1093 people with T1D from Sweden, the association between statin use and glycaemic control was evaluated.

2 In the multivariate analysis, after adjustment for a myriad of confounding factors, including demographics, metabolic markers and antihypertensive therapy, statin use was independently associated with an increase in HbA_{1c} of 2.0 mmol/mol (0.2%; P=0.029).

3 Statins have previously been linked to a greater risk of type 2 diabetes, possibly as a result of decreased insulin sensitivity. This is in keeping with the current results in people with type 1 diabetes; however, the authors point out that causality cannot be inferred from their study.

4 They also state that, given statins' benefits in terms of cardiovascular outcomes, their findings should not lead to discontinuation of the drugs; rather, they recommend re-evaluation of insulin doses when an individual begins statin treatment.

Jensen MT, Andersen HU, Rossing P, Jensen JS (2015) Statins are independently associated with increased HbA_{1c} in type 1 diabetes – The Thousand & 1 Study. *Diabetes Res Clin Pract* **111**: 51–7

References from commentary

Gillespie EL, White CM, Kardas M et al (2005) The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* **28**: 2261–6

Hermida RC, Ayala DE, Mojón A, Fernández JR (2012) Sleep-time blood pressure as a therapeutic target for cardiovascular risk reduction in type 2 diabetes. *Am J Hypertens* **25**: 325–34

Hermida RC, Ayala DE, Mojón A, Fernández JR (2016) Sleep-time BP: prognostic marker of type 2 diabetes and therapeutic target for prevention. *Diabetologia* **59**: 244–54

Portaluppi F, Tiseo R, Smolensky MH et al (2012) Circadian rhythms and cardiovascular health. *Sleep Med Rev* **16**: 151–66

Putnam K, Shoemaker R, Yiannikouris F, Cassis LA (2012) The renin–angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. *Am J Physiol Heart Circ Physiol* **302**: H1219–30