Cardiovascular journals

Is indapamide as effective as enalapril in reducing microalbuminuria?

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Microalbuminuria is a predictor of adverse renal and cardiovascular outcomes in people with type 2 diabetes, and is strongly associated with the presence of hypertension. Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce microalbuminuria and improve cardiovascular outcomes, and angiotension-receptor antagonists (ARAs) have been shown to reduce microalbuminuria and slow the progression to macroalbuminuria.

The NESTOR study was a comparison of indapamide 1.5 mg and enalapril 10 mg in over 500 patients with type 2 diabetes, hypertension and microalbuminuria. The study design was to show non-inferiority of indapamide against enalapril over one year.

The reduction in mean urinary albumin:creatinine ratio was the same, and to that extent the study was positive. So does this cast doubt upon the importance of the renin-angiotensin system in mediating microalbuminuria in type 2 diabetes? Careful analysis of the results shows that this is not the case. Importantly, the drop in systolic blood pressure was greater with indapamide. Indapamide, a diuretic, has its major hypotensive effect at the dose used in the study, but the dose of enalapril was suboptimal and there is a further argument that enalapril does not provide 24-hour blood-pressure control.

In the indapamide group, 40 % improved to normoalbuminuria, 51% maintained microalbuminuria and 9 % deteriorated to macroalbuminuria. The respective figures for enalapril were 42 %, 52 % and 6 %. The differences were not significant because of the small numbers, but it is interesting to speculate what would have happened with a larger, longer study using bigger doses of enalapril.

A better designed study was MARVAL, which compared valsartan, an ARA and amlodipine over a similar time period (Viberti et al, 2002). Blood pressure changes were similar with the two drugs, and it could be estimated that roughly half of the reduction in albumin excretion with valsartan was blood-pressure mediated, and half was mediated by other mechanisms. The most that can be said of NESTOR is that indapamide is as effective as suboptimal doses of enalapril.

Viberti G, Wheeldon NM, for the MicroAlbuminuria Reduction with VALsartan (MARVAL) Study Investigators (2002) Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus. A blood pressure-independent effect. *Circulation* **106**: 672–78

CIRCULATION

ED associated with silent coronary artery disease

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓

1 This study evaluated whether erectile dysfunction (ED) is associated with asymptomatic coronary artery disease (CAD) in patients with type 2 diabetes.

2 The prevalence of ED was evaluated in 133 men with type 2 diabetes with angiographically verified silent CAD and in 127 men with type 2 diabetes who did not have CAD.

3 The prevalence of ED was significantly higher in patients with silent CAD than in those without.

4 ED appeared to be the most efficient predictor of silent CAD, compared with other risk factors such as smoking and microalbuminuria.

5 The study shows a strong and independent association between ED and silent CAD in patients with apparently uncomplicated type 2 diabetes.

6 ED may become a potential marker to identify those patients with diabetes who should be screened for silent CAD.

Gazzaruso C, Giordanetti S, Amici ED et al (2004) Relationship between erectile dysfunction and silent myocardial ischaemia in apparently uncomplicated type 2 diabetic patients. *Circulation* **110**: 22–26

JOURNAL OF HYPERTENSION

Indapamide effectively reduces microalbuminuria

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓

1 The NESTOR study was designed to test whether microalbuminuria in patients with type 2 diabetes and hypertension is primarily dependent on the severity of hypertension, and to compare the effectiveness of the antihypertensive drugs indapamide and enalapril in reducing microalbuminuria.

2 After four weeks of placebo, 570 patients with type 2 diabetes, essential hypertension and persistent microalbuminuria were allocated randomly to groups to receive indapamide 1.5 mg or enalapril 10 mg once a day. Amlodipine, atenolol, or both, were added if necessary to achieve the target blood pressure of 140/85 mmHg.

3 There was a significant reduction in the urinary albumin:creatinine ratio. Mean reductions were 35 % in the indapamide group and 39 % in the enalapril group.

4 The reductions in mean arterial pressure were 16.6 +/- 9.0 mmHg for the indapamide group and 15.0 +/- 9.1 mmHg for the enalapril group; the reduction in systolic blood pressure was significantly greater with indapamide.

5 Indapamide-based therapy is equivalent to enalapril-based therapy in reducing microalbuminuria with effective blood pressure reduction in patients with hypertension and type 2 diabetes.

Marre M, Puig JG, Kokot F et al (2004) Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: the NESTOR study. *Journal of Hypertension* **22**: 1613–22

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Insulin resistance more prevalent in patients with IDCM

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓

1 This study was designed to quantify the prevalence of abnormal glucose tolerance and insulin resistance in 43 patients with idiopathic dilated cardiomyopathy (IDCM).

2 Plasma glucose responses were higher during the oral glucose tolerance tests in patients with IDCM, associated with significantly higher plasma insulin concentrations following the oral glucose challenge. In addition, abnormalities of glucose tolerance were significantly more common in patients with IDCM.

3 Insulin resistance and abnormal glucose tolerance are more prevalent in patients with IDCM and represent potentially reversible metabolic derangements in these patients.

Witteles RM, Tang WHW, Jamali AH (2004) Insulin resistance in idiopathic dilated cardiomyopathy. *Journal of the American College of Cardiology* **44**: 78–81

AMERICAN JOURNAL OF CARDIOLOGY

Unrecognised MI in patients with diabetes

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓

1 Patients with diabetes are considered susceptible to the development of clinically unrecognised myocardial infarction (MI). The Irbesartan Diabetic Nephropathy Trial provided an opportunity to evaluate the incidence of clinically unrecognised Q-wave MI in 1387 patients with type 2 diabetes and with hypertension and nephropathy.

2 During a mean follow-up of 2.5 years, 14 of 99 first non-fatal MIs in this group were clinically unrecognised, accounting for 14 % of all first non-fatal MIs. Clinically-unrecognised Q-wave MI remains a significant clinical occurrence despite the link between diabetes, hypertension, nephropathy and coronary events.

Aguilar D, Goldhaber SZ, Gans DJ et al (2004) Clinically unrecognised Q-wave myocardial infarction in patients with diabetes mellitus, systemic hypertension and nephropathy. *American Journal of Cardiology* **94**: 337–39

AMERICAN JOURNAL OF CARDIOLOGY

CKD worsens PCI outcome in patients with diabetes

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓

1 Chronic kidney disease (CKD) is a frequent complication of diabetes. However, the role of CKD in outcomes of patients with diabetes who have undergone percutaneous coronary intervention (PCI) has not been studied specifically.

2 Of 1575 patients with diabetes who underwent PCI, 1046 had preserved renal function, 492 had CKD without dialysis and 37 were dependent on dialysis.

3 Patients with CKD had more in-hospital complications. The one-year mortality rate was higher ($p<0.0001$) in patients with CKD who did not receive dialysis (16 %) and those on dialysis (44 %) compared with the group with preserved renal function (5 %).

4 CKD was associated with significantly worse short- and long-term outcomes.

Nikolsky E, Mehran R, Turcot D et al (2004) Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *American Journal of Cardiology* **94**: 300–05

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Hypertension changes platelet physiology

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓

1 The increased risk of target organ damage (TOD) in hypertension may be related to a prothrombotic/ hypercoaguable state, with abnormalities in platelets, such as increased expression of P-selectin (pP-sel and soluble sP-sel).

2 The authors studied 199 patients with hypertension; 125 had TOD. Values obtained were compared with those from 59 healthy, normotensive control patients.

3 Hypertensive patients had a higher mean platelet volume, mass, pP-sel, sP-sel and β-thromboglobulin and lower platelet granularity, but a similar platelet count, as compared with controls.

4 Within the hypertensive group, those with evidence of TOD had significantly larger platelets with greater mass but had lower granularity, sP-sel and pP-sel levels than those without TOD, possibly reflecting increased aspirin use.

5 Patients with hypertension have evidence of changes in platelet physiology, as reflected by a higher level of pP-sel.

6 Patients with TOD also had larger platelets, with greater mass, and the use of aspirin lowered pP-sel and sP-sel levels.

7 These changes may have implications for the pathophysiology of cardiovascular and cerebrovascular disease in hypertension.

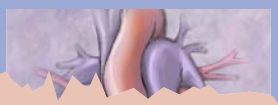
Nadar SK, Blann AD, Kamath S, Beevers DG, Lip GYH (2004) Platelet indexes in relation to target organ damage in high-risk hypertensive patients: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial. *Journal of the American College of Cardiology* **44**: 415–22

'The increased risk of target organ damage (TOD) in hypertension may be related to a prothrombotic/ hypercoaguable state, with abnormalities in platelets, such as increased expression of P-selectin...'

'Patients with hypertension have evidence of changes in platelet physiology, as reflected by a higher level of pP-sel.'

'The aim of this study was to assess the lower cutoff level of urinary albumin excretion (micro-albuminuria) associated with increased risk of coronary heart disease (CHD) and death.'

CIRCULATION



Microalbuminuria strongly predicts CHD and death

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓

1 Microalbuminuria has been suggested as an atherosclerotic risk factor. The aim of this study was to assess the lower cutoff level of urinary albumin excretion (microalbuminuria) associated with an increased risk of coronary heart disease (CHD) and death.

2 The study was performed as a substudy of the Third Copenhagen City Heart Study (1992–4); 2762 men and women aged 30–70 years underwent a detailed cardiovascular investigation programme, including a timed overnight urine sample.

3 The patients were followed up prospectively until 1999 with respect to CHD, and until 2001 with respect to death. During follow up, 109 incident cases of CHD and 276 deaths were traced.

4 A urinary albumin excretion above the upper quartile (4.8 μg/min) was associated with an increased risk of CHD and death, independently of age, sex, renal creatinine clearance, diabetes, hypertension and plasma lipids. Lower levels of urinary albumin excretion were not associated with an increased risk.

5 Microalbuminuria, defined as urinary albumin excretion >4.8 μg/min (corresponding to approximately 6.4 μg/min during daytime), is a strong and independent determinant of CHD and death.

6 The authors' suggestion is to redefine microalbuminuria accordingly and perform intervention studies.

Klausen K, Borch-Johnsen K, Feldt-Rasmussen B et al (2004) Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension and diabetes. *Circulation* **110**: 32–35

'Microalbuminuria, defined as urinary albumin excretion >4.8 μg/min (corresponding to approximately 6.4 μg/min during daytime) is a strong and independent determinant of CHD and death.'

INTERNATIONAL JOURNAL OF CARDIOLOGY

Diabetes increases hypotension during coronary occlusion

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 As diabetes may interfere with autonomic and myocardial infarction, the authors studied whether diabetes alters autonomic and haemodynamic responses to acute coronary occlusion.

2 Changes in heart rate, variability and blood pressure, and the occurrence of ventricular ectopy during a two-minute coronary occlusion were analysed in 238 patients without diabetes and 32 patients with diabetes referred for single-vessel coronary angioplasty.

3 Coronary occlusion caused a decrease in blood pressure more often in patients with diabetes.

4 Patients with diabetes often develop significant hypotension during the early phase of acute coronary occlusion.

Airaksinen KEJ, Koivikko ML, Niemela MJ et al (2004) Diabetes and haemodynamic reactions to acute coronary occlusion. *International Journal of Cardiology* **95**: 237–44

CIRCULATION

HbA_{1c} levels linked with hard carotid artery plaques

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓

1 In order to examine the association between HbA_{1c} levels and carotid artery plaque prevalence, HbA_{1c} measurements and ultrasonography of the carotid artery were performed in 5960 patients without diabetes aged 25–84 years.

2 Plaque morphology was categorised into four groups, from soft to hard plaques; HbA_{1c} was categorised into five groups, from <5 % to >6.4 %.

3 The level of HbA_{1c} was significantly related to the risk of carotid plaques, and the risk increased continuously across increasing HbA_{1c} levels.

4 The relationship depended on plaque morphology, in that HbA_{1c} was positively related to the risk of hard and predominantly hard plaques, but not to the risk of soft plaques.

Jørgensen L, Jenssen T, Joakimsen O et al (2004) Glycated haemoglobin level is strongly related to the prevalence of carotid artery plaques with high echogenicity in non-diabetic individuals. *Circulation* **110**: 466–70

AMERICAN JOURNAL OF CARDIOLOGY

Metformin decreases risk of MI in diabetes

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 Patients with diabetes undergoing coronary interventions have worse clinical and angiographic outcomes than do patients without diabetes. Metformin, an insulin sensitiser, may decrease the occurrence of these outcomes.

2 In this trial, 1110 patients with diabetes received non-sensitiser therapy and 887 received metformin. Logistic regression was used to obtain odds ratios (ORs) of any clinical event, e.g. death, myocardial infarction (MI).

3 Compared with patients on non-sensitiser therapy, those on metformin showed an adjusted OR of 0.72 for any clinical event.

4 Use of metformin in patients with diabetes undergoing coronary interventions decreased adverse clinical events, especially death and MI, compared with those not on sensitiser therapy.

Kao J, Tobis J, McClelland RL et al (2004) Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. *American Journal of Cardiology* **93**: 1347–50