Major journals

Chlorthalidone-based therapy improves long-term outcomes

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While it is recognised that diuretic-based anti-hypertensive therapy results in the development of diabetes, it is also well known that therapy results in improved clinical outcomes in patients both with and without diabetes. Previous studies have suggested that the duration of clinical trials has been too short to examine the adverse effects of diuretic therapy in patients with diabetes and hypertension.

This paper (see right) examines the long-term mortality rate of patients in the Systolic Hypertension in the Elderly Program (SHEP; n=4732). Patients were randomised to stepped care therapy with chlorthalidone 12.5–25 mg once daily or matching placebo. Further therapy to achieve blood pressure therapeutic goals included the use of atenolol or matching placebo. Subsequent to 14.3 years of follow-up, cardiovascular mortality was significantly lower in the chlorthalidone group (19%) than the placebo group (22%; adjusted hazard ratio [HR], 0.854; 95% confidence interval [CI], 0.751–0.972).

Diabetes itself was associated with increased cardiovascular mortality rate (adjusted HR, 1.659; 95% CI, 1.413–1.949) and total mortality rate (adjusted HR, 1.510; 95% CI, 1.473–1.693). Diabetes that had developed during the trial in patients who were on placebo was also associated with increased cardiovascular adverse outcomes. More importantly, diabetes that developed while patients were on diuretic therapy did not appear to have a significant association with cardiovascular mortality. Diuretic therapy in patients who had diabetes was strongly associated with a reduction in cardiovascular mortality. Consequently, chlorthalidone-based treatment appears to improve long-term outcomes – especially among patients with diabetes – and therefore may be safe to use in these patients.

AMERICAN JOURNAL OF CARDIOLOGY

Chlorthalidone improves long-term clinical outcomes

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

1 Diuretic-based anti-hypertensive treatment has been shown to improve clinical outcomes despite the development of diabetes that is associated with diuretics.

2 A possible explanation for this that had not been ruled out was that the trials in which this was established involved too short an observation period.

3 Long-term results are reported from the Systolic Hypertension in the Elderly Program (n=4732), which recorded mortality in patients with isolated systolic hypertension, with and without diabetes, who were randomised to stepped-care therapy with chlorthalidone 12.5–25.0 mg/day or matching placebo.

4 The treatment was associated with a significantly lower rate of cardiovascular (CV) mortality at a mean follow-up of 14.3 years (adjusted hazard ratio [HR], 0.854; 95% confidence interval [CI], 0.751–0.972).

5 In contrast to diabetes present at baseline, diabetes diagnosed during treatment was not associated with a significant CV or total mortality rate increase.

6 In patients with diabetes, the treatment led to significant long-term improvements in CV (adjusted HR, 0.688; 95% CI, 0.526–0.848) and total mortality rate (adjusted HR, 0.805; 95% CI, 0.680–0.952).

7 These results undermine the criticism that the observation period of previous trials was too short.

Kostis JB, Wilson AC, Freudenberger RS, Cosgrove NM, Pressel SL, Davis BR et al (2005) Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. *American Journal of Cardiology* **95**(1): 29–35

CIRCULATION

Outcomes with TZDs and metformin in patients with heart failure

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

1 The US Food and Drug Administration strongly warns against using thiazolidinediones (TZDs) in patients with diabetes who have heart failure, but prescription is still common; the adverse outcomes of this have not been documented.

2 This observational study looked at 16 417 Medicare beneficiaries (≥65 years old) discharged after heart failure.

3 Time to all-cause death was the primary outcome measure; secondary outcome measures included time to readmission for heart failure or all causes.

4 In multivariate analyses, TZDs (hazard ratio [HR], 0.87; 95 % confidence interval [CI], 0.80–0.94) and metformin (HR, 0.86; 95% CI, 0.78–0.97) were both associated with significantly lower mortality rates.

5 All-cause readmission rates were not affected by TZDs or metformin; however, readmission rates for heart failure were significantly increased with TZDs (HR, 1.06; 95% CI, 1.00–1.12) and significantly reduced with metformin (HR, 0.92; 95% CI, 0.86–0.99).

6 The authors suggest that further study to corroborate the findings is merited, as current guidelines may be depriving many patients with heart failure of major health benefits.

Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM (2005) Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* **111**(5): 583–90

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Diabetes raises risk of abnormal myocardial perfusion

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

1 Diabetes independently predicts outcomes after primary percutaneous coronary intervention for acute myocardial infarction, but whether the lower rate of myocardial reperfusion is responsible had not previously been established.

2 Reperfusion success was assessed using myocardial blush grade (n=1301) and ST-segment elevation resolution (700).

3 Patients with diabetes had a higher risk of abnormal myocardial perfusion, using both measures.

4 This higher risk may contribute to the increased rates of adverse oucomes in these patients.

Prasad A, Stone GW, Stuckey TD, Costantini CO, Zimetbaum PJ, McLaughlin M et al (2005) Impact of diabetes mellitus on myocardial perfusion after primary angioplasty in patients with acute myocardial infarction. *Journal of the American College of Cardiology* **45**(4): 508–14

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Sympathetic dysfunction linked to myocardial injury

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

1 The development of myocardial injury in diabetes is poorly understood, but potential factors include changes in cardiac sympathetic tone, innervation and responsiveness, and abnormal myocardial perfusion.

2 Sympathetic tone and myocardial perfusion were studied in healthy controls (n=10) and patients with type 1 diabetes with (n=16) and without (n=12) early diabetic microangiopathy.

3 Compared with the other groups, patients with early microangiopathy had deficits of left ventricular (LV) [^{11}C] *meta*-hydroxyephedrine retention, greater norepinephrine excursions, abnormal myocardial blood flow regulation, and LV diastolic dysfunction.

4 This led the authors to conclude that augmented sympathetic tone and responsiveness coupled with abnormal myocardial perfusion may contribute to myocardial injury.

Pop-Busui R, Kirkwood I, Schmid H, Marinescu V, Schroeder J, Larkin D et al (2004) Sympathetic dysfunction in type 1 diabetes: association with impaired myocardial blood flow reserve and diastolic dysfunction. *Journal of the American College of Cardiology* **44**(12): 2368–74

JOURNAL OF HYPERTENSION

Candesartan and enalapril are similar in their effects

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

1 This study assessed the effects of enalapril (an angiotensin-converting enzyme inhibitor) and candesartan (a highly selective angiotensin receptor blocker) on circulating adhesion molecules, which may have prognostic use as endothelial damage markers.

2 Hypertensive patients with type 2 diabetes were randomised to one of the treatments (118 completed the 24-week treatment period).

3 The two treatments reduced the level of adhesion molecules similarly (including intercellular adhesion molecule-1, the primary end point).

4 Adverse events and blood pressure lowering were also similar, but albuminuria was reduced more with candesartan.

Rosei EA, Rizzoni D, Muiesan ML, Sleiman I, Salvetti M, Monteduro C et al (2005) Effects of candesartan cilexetil and enalapril on inflammatory markers of atherosclerosis in hypertensive patients with non-insulin-dependent diabetes mellitus. *Journal of Hypertension* **23**(2): 435–44

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Reduced GFR predicts cardiac event risk increase

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

1 As diabetes is linked to a greater risk of asymptomatic coronary heart disease, there is a need for predictors of cardiac events in asymptomatic people with diabetes.

2 In this study, the predictive use of a reduced glomerular filtration rate (GFR) was examined in 269 asymptomatic patients with creatinine clearance (CrCl) and albuminuria recorded at baseline.

3 The 77 (29%) patients with a reduced GFR (CrCl<60 ml/min/1.73 m^2) had a longer duration of diabetes (P=0.002) and a higher albuminuria prevalence (P=0.04).

4 There was a two-fold increase in cardiac events in patients with reduced GFR (P=0.019) and this was shown to be independent of albuminuria in a multivariate analysis (odds ratio, 2.2; 95 % confidence interval, 1.1–4.6); albuminuria, on the other hand, was not an independent predictor.

5 Currently, the authors state, the routine use of non-invasive tests for cardiac risk in all patients who have diabetes is controversial owing to a lack of knowledge on the cost-effectiveness and the clinical benefit of early intervention.

6 This controversy could be addressed by identifying high-risk patients who would benefit from non-invasive testing, and this study suggests that a reduced GFR can be used in this way.

Knobler H, Zornitzki T, Vered S, Oettinger M, Levy R, Caspi A et al (2004) Reduced glomerular filtration rate in asymptomatic diabetic patients: predictor of increased risk for cardiac events independent of albuminuria. *Journal of the American College of Cardiology* **44**(11): 2142–8

'There is a need for predictors of cardiac events in asymptomatic people with diabetes.'

'The routine use of non-invasive tests for cardiac risk in all patients who have diabetes is controversial.'