Cardiovascular protection by β-blockade in hypertensive haemodialysis patients: the Hypertension in Haemodialysis Patients Treated With Atenolol or Lisinopril (HDPAL) trial

Carmine Zoccali and Francesca Mallamaci

Nephrology, Hypertension and Renal Transplantation Unit, and CNR (National Research Council) - IFC Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension Unit, Ospedali Riuniti, Reggio Calabria, Italy

Correspondence and offprint requests to: Carmine Zoccali; E-mail: carmine.zoccali@tin.it

In the pioneer years of chronic haemodialysis (HD), hypertension was recognized as the main undisputable cause of death in end-stage kidney disease (ESKD) patients [1]. Nearly a half-century later, sparse data in various countries indicate that control of hypertension in the HD population still remains a major unmet clinical need worldwide. In the USA, the prevalence of hypertension exceeds 80% [2], in Great Britain it is about 50% [3] and in Italy about 70% [4]. Progress in this area has been in part hindered by the ‘reverse epidemiology’ scenario that characterizes the HD population. Uncertainty about blood pressure (BP) targets and methods of measurement is such that the Renal Association guidelines cautiously state that ‘It would be sensible to avoid sustained BP extremes and, in order to try to provide some guidance, we suggest that systolic blood pressure during the interdialytic period on HD and for peritoneal dialysis (PD) patients should not regularly exceed >160 mmHg’ [3]. Low pre-dialysis BP rather than high BP is associated with death risk. Furthermore, in sharp contrast to a large meta-analysis in individuals in the general population without a background of cardiovascular events [5], the pre-dialysis relationship between BP and death risk in end-stage kidney disease (ESKD) is definitely non-linear [6]. However, peri-dialytic BP measurements are inherently inadequate metrics of the BP burden because measurements before dialysis overestimate the underlying average BP while post-dialysis BP underestimates the same parameter. In studies applying ambulatory blood pressure monitoring (ABPM) in the HD population without severe heart failure, the link between BP and clinical outcomes is comparable with that registered in the general population with the same technique [7]. Indeed, high average ambulatory systolic pressure [8] and nocturnal systolic hypertension [9] during the dialysis intervals are strong death predictors in HD patients.

Notwithstanding the public health relevance of the problem and the peculiar risk profile of the ESKD population, the number of randomized, controlled trials (RCTs) testing antihypertensive drugs in dialysis patients is very limited indeed. A meta-analysis performed in 2009 [10] identified only eight randomized trials. Of these, one was performed in patients on peritoneal dialysis, two dealt with normotensive or hypotensive patients affected by left ventricular systolic dysfunction or heart failure and another trial (FOSIDIAL) selected patients with left ventricular hypertrophy (LVH), independent of BP [11]. After this meta-analysis, the OCTOPUS trial was published [12]. Thus, we have just four relatively small RCTs specifically focusing on drug treatment of hypertension in HD patients without severe heart failure (NYHA class III or IV) (Fig. 1). Of these trials, one tested a calcium antagonist (amlodipine) [13] and three various angiotensin II receptor blockers (ARBs): candesartan in the first [14]; candesartan, losartan or valsartan in the second [15] and olmesartan in the third [12]. In trials testing ARBs, the antihypertensive effect of these drugs was comparable with that achieved by other drugs. Nonetheless, of these three trials, two documented a reduction in the risk of cardiovascular events (~47% [3] and ~71% [4]). If we consider also the FOSIDIAL trial where about half of the patients were hypertensive, the combined analysis (random-effects) of trials based on ARBs and angiotensin-converting enzyme inhibitors (ACEi) shows a 31% risk reduction [RR: 0.69, 95% confidence interval (95% CI) 0.45–1.05, $P = 0.086$], which just fails to achieve statistical significance. Because BP in patients randomized to ACEi or ARBs in these trials was almost identical to that in patients randomized to other drugs, the apparent benefit of ACEi or ARBs appears attributable to the interference with angiotensin II effects on the cardiovascular system beyond vasoconstriction. These results are similar to those of a recent meta-analysis reporting a substantial, BP-independent, benefit of ACEi and ARBs in over 100 000 high-risk patients without heart failure [16] most of whom were hypertensive.
Sympathetic overactivity is a fundamental alteration in ESKD, and this alteration per se entails a high risk for cardiovascular complications [17]. Sparse observations in ESKD indicate that propranolol is very effective for the treatment of drug-resistant hypertension in HD patients [18], and that secondary prevention in hypertensive and normotensive patients with a history of coronary heart disease [20]. These drugs and ACEi rank as the most used anti-hypertensive agents in ESKD [21], and it is therefore important to know their comparative effectiveness in this population. In this issue of the journal, Agarwal et al. report the very first study to make a head-to-head comparison of a β-blocker (atenolol) with an ACEi (lisinopril), the Hypertension in Haemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) study [22], a trial in which the primary end point was regression of LVH. This trial was recently presented at the 2013 ASN Congress in Atlanta. In the HDPAL study, hypertensive patients in the two arms of the trial were targeted to a similar BP goal by applying state-of-art ABPM and home BP measurements. Most of these patients were already on β-blockers (80% of those randomized to atenolol and 72% of those randomized to lisinopril) and on drugs interfering with the renin–angiotensin system (ACEi 57 versus 66% and ARBs 13 versus 7%), and these drugs were carefully tapered down before the trial. After a 12-month treatment period with atenolol or with lisinopril-based regimens, hypertensive patients achieved a similar fall in 44 h interdialysis ABPM (−21/−13 mmHg; −18/−10 mmHg, respectively). The reduction in dry weight was by 0.6 kg higher in the lisinopril-treated than in the atenolol-treated patients, and the use of other anti-hypertensive drugs was more frequent in the lisinopril group. Nonetheless, the risk for hospitalizations for heart failure and cardiovascular events including myocardial infarction, stroke and cardiovascular death was markedly higher in the lisinopril than in the atenolol group. Overall, the incidence rate ratio for major cardiovascular events was 2.36 higher in the lisinopril group, and the independent safety monitoring board recommended an early stop of the trial. Findings in this study are coherent with a large meta-analysis in patients with a history of cardiovascular events comparing 37 β-blocker trials with an equal number of trials based on other anti-hypertensive agents [20]. The higher rate of cardiovascular events in the lisinopril group might in part be explained by β-blocker withdrawal in this group. However, tapering was done gradually and previous treatment with β-blockers was not an effect modifier for the risk of cardiovascular events in the HDPAL study (P = 0.15, Supplementary Figure S3: sub-group analysis). Overall, it seems most likely that atenolol truly allows for better cardiovascular protection than lisinopril.

It is important to note that β-blockers are superior to central sympatholytics for countering the deadly effects of sympathetic overactivity in high-risk conditions like heart failure. Moxonidine, a centrally acting antihypertensive imidazoline receptor agonist, reduced very effectively norepinephrine levels but increased the risk of death in patients with heart failure in the Sustained Release Moxonidine for Congestive Heart Failure (MOXCON) trial [23] and the central alpha-receptor blocker prazosin showed no benefit on clinical outcomes in these patients [24]. β-Blockers modulate but do not reduce sympathetic activity. In patients with heart failure on ACE inhibitors, β-blockers do not lower underlying sympathetic nerve firing but restore low- and high-frequency harmonic oscillations in muscle sympathetic nerve activity [25]. Augmented modulation of sympathetic outflow could contribute to the beneficial effects of β-blockers in heart failure and in hypertensive dialysis patients as well. In light of the likely benefit of ACEi and ARBS in ESKD (Figure 1), it is most probable that the superiority of atenolol over lisinopril is not due to the deleterious effect of lisinopril in regard to the clinical outcomes but due to the superior cardioprotection afforded by atenolol in HD patients. As matter of fact, the overall cardiovascular events and death rates in the lisinopril group were substantially less than those registered in 2012 in the United States Renal Data System in the age range 45–65 years [26] the death rate in the lisinopril group being just 5.4% per 100 patient years, i.e. about one-third of the mortality rate...