



*Celebrating
Five Years
2003 – 2008*

KDIGO Controversies Conference

Blood Pressure in Chronic Kidney Disease Stage 5D

14-15 March, 2009

**Location: The Roosevelt Hotel
New York, NY USA**

Kidney Disease: Improving Global Outcomes (KDIGO) is an independently incorporated non-profit organization governed by an international Board of Directors with the stated mission to “improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines.” One of the initiatives determined by the Board of Directors of KDIGO is a series of international Controversies Conferences to examine what is known, what can be done with what is known and what needs to be known on controversial topics of clinical relevance in nephrology. To that end, KDIGO will facilitate a conference on “Blood Pressure in Chronic Kidney Disease Stage 5D” to be held in New York, NY on 14-15 March, 2009.

Conference Description

Epidemiological studies in general population have emphasized the close relationship between the blood pressure (BP) and the incidence of cardiovascular (CV) diseases. The relationship between BP and CV risk in general population is continuous with increased BP levels, and independent of other risk factors. Traditionally, the severity of hypertension was classified principally on the basis of diastolic blood pressure (DBP) which was considered to be the best predictor of risk. This interpretation resulted from the view that BP was the product of cardiac output and vascular resistance defining mean BP which is closer to diastolic BP than to systolic BP. Nevertheless, recent prospective epidemiological studies have directed attention to systolic pressure as a better guide than diastolic to cardiovascular and all mortality, and it has been also shown that increased pulse pressure (PP) is an independent cardiovascular risk factor in hypertension. In general populations the relationships between these different BP parameters vary significantly with age. In industrialized societies, longitudinal studies have shown that SBP increases linearly throughout the ageing, while DBP shows an increase throughout the childhood till the fifth decade followed by a late fall, with a transition at 50 to 60 years. PP thus increases markedly in later life, and isolated systolic hypertension (ISH) becomes the predominant form of hypertension in people >60 years. These changes are accompanied by an age-related shift from DBP to SBP hypertension, and finally to PP as key predictors of coronary heart disease (CHD) risk. Importantly, from age 60 years, DBP is negatively related to CHD risk. In middle-aged and elderly subjects, for any given level of SBP, those with lower DBP have greater CHD and mortality risk. In a meta-analysis of outcome trials in patients with ISH, the benefit of treatment was overwhelmingly due to the reduction in SBP rather than DBP. A further factor is that

clinical trials and epidemiological studies have shown that control of SBP is more difficult to achieve than control of DBP. Such studies have focused attention on the factors that determine the level of DBP, SBP and PP (cardiac output, peripheral resistance, arterial stiffness, time constant of the arterial system, etc). Unfortunately such studies were not done in CKD5 and ESRD populations, and the relationships between BP and CV morbidity and mortality, and BP and ageing in renal patients may be different from those observed in general populations.

Observational data in hemodialysis patients indicated an increased CV mortality associated with lower systolic and diastolic pressures, and increased mortality observed only in SBP \geq to 180 mm Hg. Low SBP is not associated with CV risk in general populations. The association of CV risk and lower SBP in ESRD is attributable to left ventricular (LV) dysfunction, but prospective studies were not done, and the relationships between low SBP and CV outcome in patients with normal LV function remain to be studied. The association of CV mortality with lower DBP cannot be attributable to changes in LV function but are (like the resulting increase in pulse pressure) a typical sign of arteriosclerotic arterial stiffening.

CKD5 and ESRD patients are most frequently characterized by an increased SBP with DBP within the normal range (<90 mm Hg) or even lower, resulting in increased PP. The increased SBP is already found in young hemodialysis population. DBP is usually higher in younger hemodialysis patients and declined with advancing age. All these changes result in a BP pattern close to that observed in older subjects in general populations, i.e., isolated (or predominant) systolic hypertension, and attributable to “accelerated ageing” in ESRD. The definition of BP targets and normotension in ESRD is not defined and in the absence of prospective controlled interventional studies, values accepted for general populations (<140/90 mm Hg) cannot be extrapolated to uremic patients.

The pathophysiology of this BP pattern is complex implicating 3 principal factors: cardiac function (stroke volume), arterial stiffness (large arteries), and intensity of wave reflections (principally vasomotor tone of resistive arterioles). The complexity explains the difficulty of the therapy and optimized approach.

In general populations with systolic hypertension the use of diuretics is an effective treatment. The control of overhydration in ESRD patients is also of primary importance. Overhydration and sodium retention plays a role not only by volume overload, but also by nonhemodynamic direct effects on the left ventricle and vascular system (oxidative stress, production of ouabain-like substances, profibrotic effects, etc). The effective control of overhydration is of primary importance but not easy to achieve in the presence of arterial stiffening. The principal characteristic of arterial stiffness is a very steep slope of the pressure-volume relationships. Small increase in stroke volume induces large increase in systolic pressure, but during diastolic interval the diastolic run-off is followed by abrupt fall in diastolic pressure. This is responsible for hemodynamic instability during dialysis and the frequency of acute hypotensive episodes. In ESRD patients the optimal hydration and the way to obtain it safely remains to be determined in controlled studies. We know that in these patients low hourly ultrafiltration rate (longer dialysis

treatment time) or daily dialysis could achieve these goals but better definition of these parameters would be of great help.

The patients at greatest risk in a vicious cycle (fluid overload → problems in removing fluid → further fluid overload) are those who begin dialysis with low predialysis blood pressures as the result of severe cardiac failure. The prognosis of these patients is very poor because fluid can be removed only very slowly in such patients. To further aggravate this situation, dialysis patients often have diastolic dysfunction. In these patients, even a small decrease in filling pressure following dialysis ultrafiltration may result in decreased cardiac output and hypotension. As a result, fluid accumulation progresses inexorably. In addition, autonomic neuropathy complicating uremia and diabetes with inadequate peripheral arteriolar tone reactivity further increases the risk that hypotension occurs when the patient is still fluid overloaded.

While the importance of salt regulating fluid balance by dietetic means and avoidance of sodium loading during dialysis has received major emphasis, sodium has also been proposed as a uremic toxin with specific effects stimulating oxidative stress. Possibly related to this is the finding that excess sodium may be stored nonosmotically at concentrations of 180 to 190 mEq/L in skin, connective tissue, cartilage, and bone, possibly bound to glucosaminoglycans. Under various circumstances, this sodium could be intermittently released into the circulation causing hypervolemia and oxidative stress.

There are 3 major questions that must be answered if overhydration and its widespread prevalence in dialysis populations are to be improved: (1) What are the reasons for accumulation of salt and water? (2) What are the problems in removing this excess fluid load? and (3) How can a dialysis prescription be constructed to calculate the appropriate ultrafiltration of total volume and rate?

A further consequence of permanent hypervolemia and an activated renin-angiotensin system is hyperactivity of the sympathetic nerve system (SNS). In addition factors such as renal ischemia, chronic inflammation, obesity, nocturnal hypoxia and elevated levels of asymmetric di-methyl-arginine (ADMA) contribute to this increased sympathetic activity.

The sequelae are elevated arterial pressure, cardiac arrhythmias, increased myocardial oxygen demand and in concert with arterial hypertension a reduced compliance of large arteries. In addition to its volume effects, sodium exerts direct pro-fibrotic effects with the potential of aggravating kidney and cardiovascular diseases. Salt directly increases oxidative stress and is associated with the secretion of an endogenous ouabain-like substance from the adrenal gland. This digitalis-like compound induces myocardial cell hypertrophy *in vitro* and correlates with left ventricular mass (LVM) in HD patients, independent of arterial pressure and delivered dialysis dose.

More difficult seems to be the control of arterial stiffness. Arterial stiffening is the consequence of ageing and degenerative changes in the arterial walls. This phenomenon is accelerated in ESRD patients, frequently associated with extensive arterial calcifications. Few controlled interventional studies have been done in this population.

Finally, the intensity of wave reflections could be achieved with vasodilating drugs (calcium channel blockers, ACE inhibitors, nitrates) but once again the efficacy of these treatments on BP profiles and clinical outcomes in ESRD patients is poorly documented.

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<i>Celebrating Five Years 2003 – 2008</i>	

Conference Program

Friday, March 13

8:00 – 9:30 pm

8:00 – 9:30 pm	Welcome Reception	<u>LOCATION</u> State Suite
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DAY 1 AGENDA

Saturday, March 14

07:30 am – 6:00 pm

7:30 – 8:00 am	Continental Breakfast	<u>LOCATION</u> (Outside Terrace Ballroom)
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Introduction: Meeting Overview Terrace Ballroom

8:00 – 8:30 am	Welcome and Introductions Bertram Kasiske
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8:30 - 8:40 am	KDIGO – Past, Present, and Future Kai-Uwe Eckardt
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8:40 – 9:00 am	Objective and Output of the Meeting Nathan Levin and Gérard London
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Plenary Sessions:

Session Moderators: Nathan Levin and Gérard London

(Each speaker provides a 20 minute presentation followed by 10 minutes discussion time)

- 9:00 – 9:30 am **Natural history of low systolic blood pressure and blood pressure changes as an indication of future morbid events**
Presenter: Peter Kotanko
- 9:30 – 10:00 am **Hypertension, diabetes, chronic kidney disease and carotid-intima media damage; methods for identification, prophylaxis and management. Blood vessel damage and hypertension; how best to assess endothelial dysfunction?**
Presenter: Gérard London
- 10:00 – 10:30 am **BP measurement, interdialytic hypertension and the role of salt**
Presenter: Rajiv Agarwal
- 10:30 – 10:50 am **Break**
- 10:50 – 11:20 am **What is known from clinical trials about optimal drug management of hypertension in CKD Stage V – the role of beta blockers, and various forms of inhibition of the RAAS?**
Presenter: Hermann Haller
- 11:20 – 11:50 am **How best to control salt overload in hypertension? Dietetic? Aligning dialysate sodium with patient's serum sodium, prohibition of sodium profiling**
Presenter: Ken Farrington
- 11:50 – 12:10 pm **Non osmotic sodium in the body; significance and management**
Presenter: Jens Titze
- 12:10 – 1:00 pm **Lunch**
- 1:00 – 1:30 pm **Hypertension and raised hematocrit, relationship to EPO and volume contraction**
Presenter: Kai-Uwe Eckardt
- 1:30 - 2:00 pm **Hypertension and sleep apnea in CKD Stage 5**

Presenter: Chris Chan

2:00 – 2:30 pm

Discussion and intro to break out sessions

2:30 – 3:00 pm

Break

LOCATION

3:00 – 6:00 pm

Breakout Sessions

Group One: Optimal BP target in relation to end-organ damage in dialysis patients **Terrace Ballroom**

Discussion Leaders: Peter Kotanko and Carmine Zoccali

Group Two: Pharmacologic therapy to achieve BP targets **Riverside Suite (2nd Floor)**

Discussion Leaders: Josep Redon and Alfred Cheung

Group Three: Non-pharmacologic therapy to achieve BP targets - focus on volume and salt control **Fifth Ave Suite (2nd Floor)**

Discussion Leaders: Charles Chazot and David Wheeler

6:00 pm

Adjourn (Workgroup Discussion leaders meet to develop presentation on recommendations)

7:30 – 9:30 pm

Group Dinner at the Ammos Restaurant
Meet in hotel lobby 7:15 pm



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DAY 2 AGENDA

Sunday, 15 March

7:30 am to 3:30 pm

LOCATION

7:30 – 8:00 am	Continental Breakfast	
8:00 – 9:00 am	Breakout Sessions Resume	
	Group One: Optimal BP target in relation to end-organ damage in dialysis patients	Terrace Ballroom
	Discussion Leaders: Peter Kotanko and Carmine Zoccali	
	Group Two: Pharmacologic therapy to achieve BP targets	Riverside Suite
	Discussion Leaders: Josep Redon and Alfred Cheung	
	Group Three: Non-pharmacologic therapy to achieve BP targets - focus on volume and salt control	Fifth Ave Suite
	Discussion Leaders: Charles Chazot and David Wheeler	
9:00 – 10:00 am	Break/Checkout (Breakout Group Leaders finalize presentation on recommendations)	
	Presentation and Discussion of Recommendations (Breakout group discussion leaders provide 20-30 presentations on recommendations from their group, followed by 30 minute discussion period)	
10:00 – 11:00 am	Group 1 Presentation	Terrace Ballroom
11:00 – 12:00 pm	Group 2 Presentation	

12:00 - 1:00 pm	Group 3 Presentation
1:00 - 1:45 pm	Working Lunch
1:45 - 3:00 pm	Discussion and consensus on recommendations
3:00 - 3:30 pm	Wrap up and outline of tasks for drafting of position statement
3:30 pm	Adjourn (Departures)