Cardiovascular prevention by nocturnal haemodialysis
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Slide 1

Disclosure of Interest

ALI BASCI

Formal association with a company:
Fresenius Medical Care Dialysis Service

The details of each Disclosure of Interest are available at the Invited Speakers' desk (located in the Registration Area).

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Thank you very much Chairman, dear colleagues. First of all, I would like to thank ERA-EDTA for bringing this beautiful congress to our city and our country.

I would like to go back to first practice base of the haemodialysis. In the early 60s, long dialysis started, about 20 or 40 hours weekly and generally, in hospital first and later it moved home because of the increasing number of patients in hospital.
In the early era of chronic dialysis with 20-40 h/week HD

- Excellent BP control, rare intradialytic BP drop
- Satisfactory nutritional status
- Sufficient RBC production
- Nearly full rehabilitation, almost no neuropathy

In the early era of chronic dialysis: long performance, excellent blood pressure control, intradialytic blood pressure drops unknown even, satisfactory nutritional status, sufficient red blood cell production, nearly full rehabilitation, almost no neuropathy.
“Intensive utilisation of a dialysis unit”
- From 27 hour/week in 1971 to 12 hour/week in 1972
- Successful adaptation, similar biochemical results “except phosphate”
  Cambi V. Proc Eur Dial Transplant Assoc 1973; 10: 342

Short dialysis schedules – “Finally ready to become a routine ?”
- Although “bilateral nephrectomy is required in 2 cases for BP control”
  Proc Eur Dial Transplant Assoc 1973; 10: 342-8

the society needed an intensive utilisation of the dialysis unit. In the early 70s, it got shorter but after that half the duration and with this type of performance successful adaption, similar biochemical status except phosphate. But when short dialysis schedule became routine, blood pressure control was not so good and sometimes

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- Why dialyze more than 6 hours a week?
  Rotellar E, ASAIO Trans 1985; 31:538

How long should it be ? Need for a scale ?

- “God sent Kt/V for short hemodialysis”
  Twardowski ZJ, University of Missouri

Despite presence of hypertension, hyperphosphatemia, anemia, “dialysis is adequate if Kt/V is above ...”

they needed to have bilateral nephrectomy.

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And now we face:

Problems in patients treated with three times weekly four-hour hemodialysis

So, with this short dialysis, I mean 3 times weekly 4 hour haemodialysis

- High mortality and morbidity, low QOL
- Numerous troubles
  - High/low BP, LV hypertrophy, heart failure, arrhythmia
  - Anemia, malnutrition, inflammation
  - Hyperphosphatemia, vascular calcification

USRDS, Am J Kidney Dis 2003; 42 (Suppl 5): S103

- Introduction of several medications to solve these problems (Epo, P-bindres, ACE-I, carniten, gabapentin, etc)
  - Extra cost (equal to 1/4 to 1/2 of dialysis cost)
  - No survival benefit with these medications
we faced some problems.

The problems we had were of course, high blood pressure and cardiovascular comorbidity and quality of life, a worse quality of life and we needed some efficient tools to improve the outcome of haemodialysis. We introduced some drugs to correct the problems, ACE inhibitors, statins and non-calcium based phosphate binders and so on but none of those had any benefits.

So, we needed more efficient haemodialysis. We can increase the Kt/V, the HEMO study for example, no survival benefit. More frequent HD sessions, longer HD sessions, more frequent and longer HD sessions at home.
We know that long dialysis may produce better uremic toxin clearance in standard and long dialysis in this study here. We can see here all the uremic toxins are lower cleared in long dialysis.

The Japanese registry also showed that even if 1 hour less dialysis may increase the risk of mortality 4 times, the shorter haemodialysis, the higher mortality.
We discovered the duration of HD sessions and mortality from the Dutch study too. We know that even 30 minutes less dialysis may cause a 35% risk of no mortality.

In three times weekly HD, best survival with 8-h sessions

Also, this is a well-known sample from Tassin; Tassin used an in-centre long dialysis best survival compared to the other registries.
We can also look at the transplantation. In the study survival in nocturnal HD similar to the cadaveric donor transplantation. Here, this is the liver transplantation and this is the cadaveric transplantation.

**Advantages of Long HD**

- **NHD**
  - BP control: +++
  - LVH: +++
  - LV systolic functions: +++
  - Arterial compliance: +++
  - Sleep apnea: corrected

*Perl J, Am J Kidney Dis 2009; 54: 117-84*

So long dialysis provides us with better blood pressure control, low left ventricular hypertrophy better and left ventricular systolic function is better. Arterial complement is better and sleep apnoea was corrected in this study.
This prospective randomised controlled trial, this is 5-6 nights a week at home, more than 6 hours haemodialysis compared to conventional HD. Clearly, we can see here better blood pressure, less anti-hypertensive drugs and perfect control of phosphate without phosphate binders and left ventricular mass significantly decreased in 6 months.

Best survival data with three times weekly HD from Tassin: 8-h in-center HD
- Excellent patient survival (5-year survival 87%)
- Very few hypertension, good phosphate control, less anemia

Kidney Int 1992; 41: 1286

No prospective study to compare hemodialysis regimens applied in the past and now

Frequent Hemodialysis Network randomized trials: conventional HD versus in-center short daily HD and versus home nocturnal HD

Suri RS, Kidney Int 2007

Best survival data with 3 times weekly HD from Tassin. 8-hour in-centre dialysis. Excellent patient survival, 5-year survival is 85-87% as you know, very little hypertension, good phosphate control, less anaemia. No prospective study to compare the haemodialysis regimen applied in the past and now. Frequent Haemodialysis Network randomised trials are conventional haemodialysis versus in-centre short daily haemodialysis versus home nocturnal HD.
This study showed that in many measures are favourable but non-access hospitalization and death is not favourable.

Our long dialysis study first presented in ASN in 2008
Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis

Ercan Ök1, Sener Duman1, Gulay Asci1, Murat Tumüskü2, Ozen Ozen Sertoğ3, Meral Kayıkçıoğlu4, Huseyin Toz1, Siddik M. Adam1, Mுmtaz Yılmaz1, Halil Zeki Tonbul5, Mehmet Ozkahya6 and On behalf of the ‘Long Dialysis Study Group’

1Division of Nephrology, Ege University School of Medicine, Izmir, Turkey; 2Department of Cardiology, Konya Hospital, Konya, Turkey; 3Department of Psychiatry, 4Department of Cardiology, Ege University School of Medicine, Izmir, Turkey; 5Division of Nephrology, Adana Training and Research Hospital, Adana, Turkey and 6Division of Nephrology, Selçuk University School of Medicine, Konya, Turkey

and also published in NDT.

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- Prospective, matched-controlled study to compare 8-h and 4-h in-center HD; follow-up one year
  ClinicalTrials.gov Identifier: NCT00413803

- 247 prevalent conventional HD patients were assigned to 8-h three times weekly in-center nocturnal HD (NHD)

- 247 age-, sex-, diabetic status-, and HD vintage-matched control cases to 4-h conventional HD (CHD)

- No difference in baseline parameters
This was a prospective matched-control study to compare 8-hours, 4-hours in-centre HD followed for 1 year. 245 prevalent conventional HD patients were assigned to 8 hours 3 times weekly in-centre nocturnal HD. 257 age, sex and diabetic status and HD vintage matched-control cases to 4-hour conventional HD, no difference in baseline parameters.

These are the flow charts and we're talking about almost 1200 patients who had nocturnal haemodialysis, long dialysis very good to better understand. But only a quarter of them accepted. Remember this is the in-centre study not the home study. So, they don't want to sleep out of their home of course. Later also with the inclusion criteria the number comes to 247 and also we allocated the other matched-control groups with conventional group.

The baseline finding is almost the same but duration is two times more. Blood flow of course, is lower in the nocturnal group.
12-month survival was better in the nocturnal group. Death rate also is better in the nocturnal group.

<table>
<thead>
<tr>
<th></th>
<th>NHD</th>
<th>CHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 month-survival (%)</td>
<td>98.7</td>
<td>93.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Death rate (n/100-pl-yr)</td>
<td>1.29</td>
<td>6.03</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

- Multivariate analysis
  - **NHD vs CHD**: 0.23 (0.06-0.80) 0.02
  - **Age (per 1 year)**: 1.07 (1.03-1.11) <0.001

* Adjusted for age, gender, diabetes, and HD duration
Model Chi-square: 24.3, p<0.001

73% less all-cause hospitalization rate in the NHD arm (p<0.05)
Marked decrease in intradialytic hypotension episodes in the NHD group (p <0.01)

73% less all-cause hospitalization rate in the nocturnal arm, a marked decrease
Mineral metabolism was also better especially as expected phosphate control very good and of course, this can be achieved without much using phosphate binders.
In 6 months, the phosphate binder use dropped and later stabilised and the other parts of course, conventional ones higher phosphate control.

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<table>
<thead>
<tr>
<th></th>
<th>Nocturnal HD (n=227)*</th>
<th>Conventional HD (n=242)*</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Anemia control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.8±1.4</td>
<td>11.4±1.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>783±617</td>
<td>893±714</td>
<td>0.08</td>
</tr>
<tr>
<td>Transferrin sat (%)</td>
<td>27.2±14.4</td>
<td>31.7±16.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Epo use (% at 12th mo)</td>
<td>24.7</td>
<td>53.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV iron use (% at 12th mo)</td>
<td>63.1</td>
<td>57.4</td>
<td>0.35</td>
</tr>
<tr>
<td>SC Epo dose (U/week)</td>
<td>1697±2102</td>
<td>2819±2397</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV iron dose (mg/week)</td>
<td>26±33</td>
<td>20±21</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Anaemia control is also very good but using less EPO or less EPO dose.

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Here you can see the EPO is decreasing over time.

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**Three HD Center Observational Study**

- N= 218 (F/M:86/132)
- Age (mean at the time start HD):48±15 years
- Diabetic 24 (%11) nondiabetic 194
- ESRD etiology GN %23, TIN %16 PKD %8, DN %11 Other %11 Unknown %31
- HD duration mean 38 months (5-160 mo.)

Ozkahya M. Et al NDT (2006) 21:3506-3513

Blood pressure control is very important. This very small study with three satellite centres next to my university hospital under the control of our group. This is of course an unusual group. You see this is the relatively young group, the diabetics are low and so on.

**Slide 34**
But we are doing this strict volume control strategy and also strict salt restriction. We train the patient at the beginning of their dialysis life. You can see here very low, most patients have no high blood pressure.

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Also, hypertension is low but this group has excellent graft survival. But this is of course, age
is predictive here but also simple tests: CT cardiothoracic index for example, some predictive data. If there is no cardiac enlargement, you have better results.

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**Blood pressure control**

- No change in mean arterial BP in both arms
- Requirement of anti-hypertensive medication decreased from 24% to 8% in the NHD group
- Increase in post-dialysis body weight in NHD group, with stable blood pressure (from 65±14 to 67±15 kg, p<0.001)

We are coming back to the long dialysis study and on both sides there is better blood pressure control, similar but extremely lower usage of the anti-hypertensive drugs in the blood pressure in the nocturnal group.

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**Cardiac structure**

- Decrease in LA diameter in the NHD group (from 2.35 ± 0.40 mm/m² BSA to 2.17 ± 0.34, p<0.001)
- Regression in LV mass index in the NHD group (from 140 ± 44 g/m² BSA to 116 ± 34, p<0.001)
Of course, also cardiac structure is different. A decrease in the left atrium diameter in the nocturnal group and regression in left ventricular mass index in the nocturnal group.

### Slide 38

<table>
<thead>
<tr>
<th>Nutrition-inflammation</th>
<th>Nocturnal HD (n=227)*</th>
<th>Conventional HD (n=242)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-HD body weight (kg)</td>
<td>66.6 ± 14.4</td>
<td>65.2 ± 14.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.02 ± 0.24</td>
<td>3.94 ± 0.29</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>174 ± 41</td>
<td>165 ± 42</td>
<td>0.03</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>209 ± 136</td>
<td>184 ± 117</td>
<td>0.04</td>
</tr>
<tr>
<td>hsCRP (mg/dl)</td>
<td>1.40 ± 1.37</td>
<td>1.67 ± 1.71</td>
<td>0.06</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>23.8 ± 1.7</td>
<td>23.1 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The nocturnal group also has better nutritional status.

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- Increase in serum albumin level (from 3.95 ± 0.29 to 4.10 ± 0.29 g/dL, p<0.0001)
and serum albumin level also increased in the nocturnal group better than in the conventional group.

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### The effect of longer HD on progression of coronary artery calcification

- Two multi-slice CTs in 89 patients with an interval of 10 months (43 NHD, 46 CHD)
- Followed for at least 6 months in the Long Dialysis Study
- Baseline demographical, clinical, laboratory data similar
- In follow-up serum P, CaxP product, use of P-binder and BP medication were lower in the NHD group

Asci G. et al. NDT (2011)26:1010-1015

We did a CT scan some on those patients the for coronary artery calcification. This is the practical reason of course, in two cities Aydin and Izmir we repeated for at least 6 months all demographical and clinical laboratory data similar in these groups. In follow up serum calcium phosphate products, use of phosphate binders, blood pressure medication were lower in the nocturnal group of course.

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### Change in median CAC score in patients with baseline score >200

- **Delta median CACs** (interquartile range)
  - NHD: 141 (67-291)
  - CHD: 372 (142-695)
  - p <0.01

- Lower progression rate with NHD in patients with moderate to severe vascular calcification
- Serum phosphate was predictor for CAC progression
  (Exp-B 2.05, 95% CI 1.46-2.90, p <0.001)

When we see the graph here, the delta median CAC is lower in the nocturnal group, normal progression rate in the nocturnal group in patients with moderate severe vascular
Serum phosphate is a predictor. Also the arterial stiffness has also already been published. Pulse wave velocity decrease in the nocturnal group and augmentation index decreased in the nocturnal group. Serum phosphate is predictive for change in pulse wave velocity.
Here also the pulse wave in numbers, here after 12 months 11-9.4.

**Pulse wave velocity**

- **NHD**
  - Baseline: 11.4±2.7
  - 12th month: 9.4±1.9
  - p: <0.001

- **CHD**
  - Baseline: 9.7±2.4
  - 12th month: 9.4±2.0
  - p: 0.368

- Pulse wave velocity decreased in the NHD group

_Széz M et al, Atherosclerosis 2012; 220: 477_

Diastolic dysfunction assessed by the ejection duration improved in the nocturnal HD group. Serum phosphate was a predictor for change of ejection duration.

**Ejection duration**

- **NHD**
  - Baseline: 295±33
  - 12th month: 282±34
  - p: 0.007

- **CHD**
  - Baseline: 297±29
  - 12th month: 303±34
  - p: 0.155

- Diastolic dysfunction assessed by “ejection duration” improved in the NHD group
- Serum P was predictor for change in ejection duration (β- coefficient 0.415, t 3.25, p <0.01)

_Széz M et al, Atherosclerosis 2012; 220: 477_
Subendocardial perfusion

- Subendocardial perfusion reflected by “subendocardial viability ratio” increased in NHD
- Predictors for improvement were lower CRP and NHD ($\beta$-coefficient -0.397, $t$ -3.45, $p < 0.01$) ($\beta$-coefficient 0.314, $t$ 2.70, $p < 0.01$)

Szisz M et al, Atherosclerosis 2012; 220: 477

Subendocardial reperfusion reflex by subendothelial viability ratio increased in nocturnal HD. Predictor for improvements were lower for CRP and nocturnal HD of course.

The effect of longer HD on volume and nutrition status - BIA

- Multi-frequency bio-impedance analysis in 122 patients at baseline and 12th month (5, 50, 100, 200 kHz) (62 NHD, 60 CHD)
- Baseline demographical, clinical, laboratory data similar
- In follow-up, higher eKt/V and serum albumin, lower serum P and hsCRP in the NHD arm


Extracellular volume also assessed by the bio-impedance analysis in 122 patients and baseline demographical clinical laboratory data were similar. In follow-up higher eKt/v and serum albumin lower in phosphate in high sensitive CRP in the nocturnal HD arm.
Extracellular fluid volume measured by bio-impedance analysis

- ECV decreased in the NHD group, increased in the CHD group


Extracellular volume decreased in the nocturnal group, increased in the conventional group.

Body fat mass and dry lean mass measured by bio-impedance analysis

- Increase in body fat mass and dry lean mass in the NHD group


The other site of course, this patient has a better appetite and body fat mass and also dry lean mass also increased in the nocturnal group getting fat.
This patient also had more appetite and ate more salt, intradialytic sodium in my impression is increased in terms of weight gain but still there is no high extracellular volume. You can see the change here, the extracellular volume of water and the other side the dry lean mass also changes as you can see here.

In parallel, of course this patient from the nocturnal group also has better blood pressure control.
This is also effective for the cardiac geometry of course, left atrial diameter and left ventricular mass also decreased in the nocturnal group.

We also performed a Holter monitoring in 60 patients for mid-week 48-hour recordings. Baseline demographical, clinical, laboratory data, everything is ok and everything is similar. Ejection fraction and left ventricular mass index are not different. In follow-up, lower use of anti-hypertensive medication and less hypotension episode in the NHD arm.

* p<0.05, ** p<0.01, *** p<0.001 baseline vs. final


Unpublished DATA

We also performed a Holter monitoring in 60 patients for mid-week 48-hour recordings. Baseline demographical, clinical and laboratory data, everything is ok and everything is similar. Ejection fraction and left ventricular mass index are not different. In follow-up, lower use of anti-hypertensive medication and less hypotension episodes in the nocturnal arm.
Premature ventricular ectopia

This scale also clearly shows that the premature ventricular ectopia disappears in the nocturnal group over time.

- Decrease in PVE at all time-points in the NHD group, no change in CHD patients

In conclusion, implementation of longer HD sessions may improve several outcomes:

- Better phosphate control, slow down in progression of vascular calcification, improvement in arterial stiffness
- Better volume and blood pressure control, regression of cardiac enlargement and left ventricular hypertrophy
- Improvement in anaemia, reduction of Epo requirement; decrease in ventricular arrhythmia

In conclusion, implementation of longer HD sessions may improve several outcomes: better phosphate control, a slowdown in the progression of vascular calcification, improvement in arterial stiffness. Better volume and volume blood pressure control, regression of cardiac enlargement and left ventricular hypertrophy. Improvement in anaemia, reduction of EPO requirement and decrease in the ventricular arrhythmias.
Conclusion

- Improvement in nutritional status
- Decrease in intradialytic complications and hospitalization
- Decrease in mortality

Also, improvement of the nutritional status, a decrease in intradialytic complications and hospitalisation is lower, decrease in mortality.

Limitations of the presented studies

- Non-randomized
- Relatively small numbers of study cases
- Relatively short follow-up
- Methods not most accurate ones (echo instead of MRI for LV geometry)
Of course, limitation of the presented studies are that they are not randomised, because we couldn't do that because we mentioned that this is good but sorry we randomised -- we should not say this we cannot do that and we prefer this way, relatively small numbers of the study cases, relatively short follow-up. Of course, method must be more accurate for example, echo instead of MRI of left ventricle diameters.

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For the cardiovascular prevention

- Dialysis, as long as possible
- Salt, as low as possible

For cardiovascular prevention dialysis as long as possible and salt as low as possible.

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I would like to thank my group of course, and also these studies done in the Fresenius network of 11 centres all over Turkey and also my group in Ege University

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Chairman: Only one question. I understand that the patients included in the study had to sleep in the centre, is that right?

Prof. Basci: Yes, they did. They didn't need any medication for sleeping. A couple of days, maybe it might take some time but later they sleep very well.

Chairman: But at the same time, I also understood there were roughly 50 patients who decided to stop the study, which means that it's not very good.

Prof. Basci: Some of those of course, dropped out because of the decline in the acceptance to continue to do nocturnal dialysis. That's the problem, of course. Of course, this should be done in home dialysis but we started these tests. Later on we continued these patients at home. There are 200 patients at home right now in Turkey.

Chairman: Thank you Professor Basci and thank the audience and I close this session sticking to the right time. Thank you very much.