

# Fresenius Medical Care Scientific Lunch Symposium at the **50th ERA-EDTA Congress**

## **Emerging Concept: High Volume Matters in Haemodiafiltration (HighVolumeHDF)**

**May 19th, 2013 Istanbul, Turkey**

Time: 12.30 - 14.15 hrs

Hall: Rumeli B

Please also visit us at our booth  
**Level B5, booth no. M7**

Cardioprotective Haemodialysis **SPOT**



**FRESENIUS  
MEDICAL CARE**

# Introduction

Online-haemodiafiltration is today a clinical reality in routine practice: in Europe, more end-stage chronic kidney disease patients are treated with this modality than with peritoneal dialysis.

The success of online-haemodiafiltration is attributed to factors other than the efficient removal of a broad spectrum of uremic toxins. Many clinical studies have shown that patients treated with online-haemodiafiltration have better anemia and phosphate control, therefore requiring less medication such as erythropoietin and phosphate binders. Additional benefits including increased haemodynamic stability as well as reduced inflammation and oxidative stress have also been well-documented.

The first indication that high substitution volumes matter in terms of impacting patient survival was provided by the DOPPS data published by Canaud et al. Since then, four prospective randomized controlled trials have addressed the significance of high convective volumes on patient survival.

This symposium aims at:

- Summarising the current evidence delineating the clinical benefits of online-haemodiafiltration.
- Presenting data from the latest clinical study designed specifically to address the impact of high-volume convective therapies on patient survival.
- Providing practical approaches of achieving high convective doses for each individual patient.

In the search for an optimal renal replacement therapy to improve dialysis patient outcomes, clinical evidence indicates that the needs of dialysis patients are best met by online-haemodiafiltration. The treatment modality not only has a sound scientific basis, but also an extended clinical experience for over two decades – and now backed by clinical studies showing improved patient survival.



A handwritten signature in black ink, appearing to read 'Stefan Jacobson'.

**Prof. Stefan Jacobson**  
(Stockholm, Sweden)



A handwritten signature in black ink, appearing to read 'Francesco Locatelli'.

**Prof. Francesco Locatelli**  
(Lecco, Italy)

## Emerging Concept: High Volume Matters in Haemodiafiltration (HighVolumeHDF)

**Chair:** Prof. Stefan Jacobson (Stockholm, Sweden)  
Prof. Francesco Locatelli (Lecco, Italy)



### **Current Evidence of Clinical Studies on Online-Haemodiafiltration**

Dr. Peter J. Blankestijn (Utrecht, The Netherlands)



### **New Clinical Evidence for High-Volume Online-Haemodiafiltration: The ESHOL Study**

Dr. Francisco Maduell (Barcelona, Spain)



### **Facilitating High Convective Doses: Which knobs to turn to achieve HighVolumeHDF?**

Prof. Bernard Canaud (Bad Homburg, Germany)

## Current Evidence of Clinical Studies on Online-Haemodiafiltration



**Dr. Peter J. Blankestijn**  
**Department of Nephrology and Hypertension**  
**University Hospital Utrecht, The Netherlands**

Dr. Blankestijn graduated from Erasmus University Rotterdam in 1981. Afterwards he worked at house officer department of general surgery Zuiderziekenhuis in Rotterdam.

Between 1982 – 1987 he worked as a resident internal medicine at the department of internal medicine at the University Hospital Rotterdam (head by Prof. Dr. M.A.D.H. Schalekamp).

Starting 1987 Dr. Blankestijn became a staff member in the department of internal medicine of the University Hospital Rotterdam (head Prof. Dr. M.A.D.H. Schalekamp) and as of 1991 he became a staff member and associate professor on the department of Nephrology and Hypertension of the University Hospital Utrecht. His PhD Thesis, obtained in 1991, was entitled: "Adrenaline and hypertension".

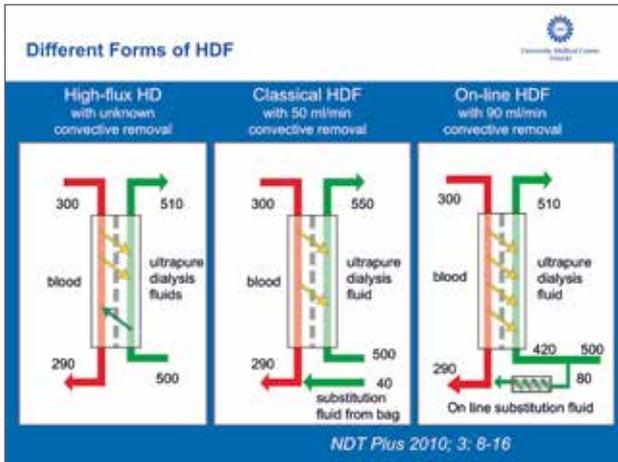
In 1992 Dr. Blankestijn has been registered as Clinical Hypertension Specialist at the European Society of Hypertension. Dr. Blankestijn has performed many research activities, which mainly included studies in humans. Main subjects of the studies are: hypertension, with special interest for hypertension in chronic, kidney disease patients and the sympathetic nervous system, treatment and prevention of complications of chronic kidney disease patients, hemodialysis techniques, as well as treatment and prevention of complications of hemodialysis treatment.

He is a principal investigator of several multicenter studies, including CONTRAST and MASTERPLAN.

Since the emergence of online-haemodiafiltration in 1985, the treatment modality has been subscribed to a steadily increasing number of patients. Other than in the USA, online-haemodiafiltration has established itself in routine clinical practice, with widespread application of this modality particularly in Europe and Japan. In fact, in Europe online-haemodiafiltration has even surpassed peritoneal dialysis as the preferred RRT option; about 15.3% of the HD patients in 2011 were treated with online-haemodiafiltration in this region.

It is important to emphasise that the appeal of online-haemodiafiltration is attributed, in the first place, to the recognition that larger uremic retention solutes need to be efficiently removed to combat the effects of uraemia. An extensive clinical experience has shown that online-haemodiafiltration also alleviates an impressive list of conditions that are associated with CKD or linked to the dialysis procedure.

In this presentation, **the key studies reporting on the several clinical benefits** attributed to online-haemodiafiltration will be summarised with respect to anemia and hypophosphatemia control, better haemodynamic stability, enhanced removal of middle molecular uremic toxins including  $\beta_2$ -microglobulin as well as curtailing the underlying mechanisms of inflammation, oxidative stress and endothelium dysfunction. Finally, the essence of studies indicating that **high convective volumes** contribute to a survival advantage for patients will be summarised.




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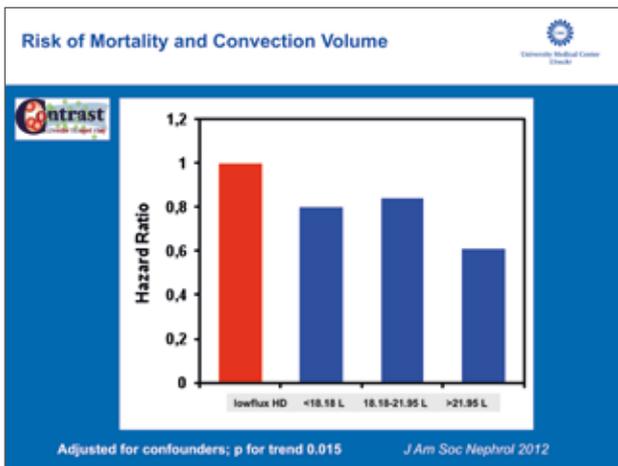
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### Studies Indicating Impact of High Convection Volume

Study Name	Authors	Threshold Volume for Survival Benefit
DOPPS	Canaud <i>et al</i>	> 15 L
CONTRAST	Grooteman <i>et al</i>	> 21.95 L
Turkish OL-HDF	Ok <i>et al</i>	> 17.4 L
ESHOL	Maduell <i>et al</i>	> 23.1 L

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## New Clinical Evidence for High-Volume Online-Haemodiafiltration: The ESHOL Study



**Dr. Francisco Maduell**  
Head Dialysis Section  
Department of the Nephrology and Renal Transplantation  
Hospital Clínic Barcelona, University of Barcelona, Spain

Dr. Maduell received his MD from the University of Barcelona, Spain in 1985. He then moved to Pamplona, Clinica Universitaria de Navarra, where he developed training in the speciality of Nephrology (1986-1989).

His doctoral thesis, which he obtained in 1990, was based on the “Alterations of the Cl-/NaCO<sub>3</sub><sup>-</sup> anion exchanger in erythrocytes of uremic patients”.

Later he worked in Hospital de Xàtiva, Hospital General Castellón and finally moved to Hospital Clínic of Barcelona where Dr. Maduell is currently Head of Dialysis Section.

In 2000 he received the prestigious award, The Outstanding Young Persons (TOYP) of the world 2000, Junior Chamber Internacional in Medical Innovation.

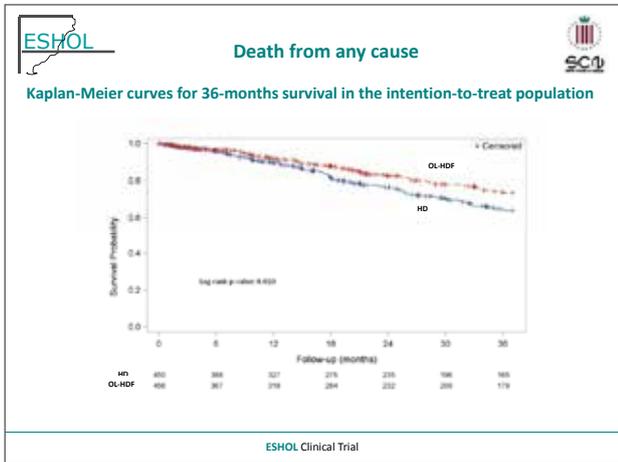
He has published more than 130 peer-review articles and more than 350 Congress presentations.

Dr. Maduell is a member of ERA-EDTA, SEN and SCN nephrology societies, and is on the editorial board of several nephrology journals. His current research interest includes dialysis adequacy, the use of hemodialysis convective treatments, daily dialysis and long nocturnal schemes and implementation of new haemodialysis devices. He is a principal investigator in numerous clinical studies.

The first indication that **mortality** rates decline with high-efficiency OL-HDF was provided by the European results from the DOPPS. Since then, the RISCAVID, CONTRAST and the Turkish HDF trials have all substantiated the original findings that higher convection volumes are favourable in terms of improved survival. Although the merits as well as the limitations of each of these studies have been discussed in detail, the collective body of evidence nevertheless points towards a survival benefit for high-volume OL-HDF. Clearly, further studies confirming the potential impact of high substitution volumes in reduction of mortality are needed.

The Spanish **ESHOL study**, a prospective randomised control trial, addressing precisely this issue has just been completed and the results are in press. This multicenter study is unique in that it was designed specifically to examine the impact of higher convective volumes on patient mortality. The findings not only support the four aforementioned studies that ascribe a survival benefit for patients, but also demonstrate that mortality rates are reduced significantly when convection volumes higher than a certain threshold identified in the study are used. The final results will be unveiled in this presentation.

Collectively, **all five studies** now indicate that a better blood cleansing effect and improvement of a number of clinical conditions afflicting the dialysis patients - achieved with the use of high substitution volumes in OL-HDF results in improved patient survival rates of end-stage CKD patients.




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**ESHOL**

### Primary outcome: Mortality

	Hemodialysis Group (n=410) (87.2 patient-years at risk)		OL-HDF Group (n=410) (86.1 patient-years at risk)		HR (95% CI)	P*
	Events	Events/100 Patient-Years	Events	Events/100 Patient-Years		
Death from any cause	122	14.1	85	9.8	0.70 (0.53-0.92)	0.01
Cardiovascular cause	55	6.3	37	4.3	0.67 (0.44-1.02)	0.06
Heart failure	18	1.2	7	0.8	0.67 (0.26-1.82)	0.46
Ischemic heart disease	15	1.2	14	1.6	0.93 (0.45-1.96)	0.86
Myocardial infarction	4	0.2	5	0.6	0.94 (0.29-3.17)	0.93
Stroke	18	2.1	7	0.8	0.39 (0.16-0.93)	0.03
Dysrhythmia	5	0.6	3	0.3	0.59 (0.14-2.47)	0.46
Peripheral vascularity	1	0.0	1	0.0	0.97 (0.06-15.48)	0.98
Infection	22	2.5	10	1.2	0.48 (0.21-0.96)	0.03
Tumor	4	0.2	10	1.2	1.67 (0.61-4.58)	0.32
Sudden death	14	1.6	14	1.6	0.99 (0.41-2.00)	0.98
Catholic	8	0.9	4	0.5	0.51 (0.15-1.73)	0.27
Death from other causes	17	2.0	10	1.2	0.59 (0.21-1.38)	0.16

Events given as no. (95% CI). HRs (95% CI) for all-cause mortality at 1, 1.1, and 1.2 point were 0.75 (0.43-1.27), 0.70 (0.53-0.92) and 0.74 (0.53-1.01), respectively. \*P value by the log-rank test.

ESHOL Clinical Trial

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**ESHOL**

### Hospitalizations and intradialysis symptoms

	Hemodialysis Group (n=410) (87.2 Patient-Years at Risk)		OL-HDF Group (n=410) (86.1 Patient-Years at Risk)		Rate Ratio (95% CI)	p*
	No. of Events	No. of Events/100 Patient-Years	No. of Events	No. of Events/100 Patient-Years		
All cause hospitalizations	412	47.9	317	36.7	0.76 (0.67-0.86)	<0.001
Infections	70	8.4	72	8.3		
Vascular access	26	11.3	50	6.5		
Heart failure	26	2.3	16	1.7		
Ischemic heart disease	25	2.9	16	1.9		
Myocardial infarction	24	3.0	28	3.2		
Stroke	10	1.2	8	0.9		
Other reasons	112	12.7	126	14.6		
Symptomatic hypotensive episodes†	8120	93.7	5562	67.2	0.72 (0.69-0.75)	<0.001
Dyspnoea‡	436	51.2	379	45.3	0.88 (0.84-0.92)	<0.001
Thirstic goal§	333	37.7	318	38.6	0.98 (0.74-1.28)	0.93

CI=confidence interval; HR=hazard ratio; HRs (95% CI) for all-cause mortality at 1, 1.1, and 1.2 point were 0.75 (0.43-1.27), 0.70 (0.53-0.92) and 0.74 (0.53-1.01), respectively. \*P value by the log-rank test. †Number of hypotensive (systolic blood pressure <90 mmHg) episodes per 100 patient-years and number of completed dialysis sessions. ‡Number of symptomatic hypotensive episodes per 100 patient-years. §Number of thirstic goal (patient-reported thirst) episodes per 100 patient-years. ††Number of thirstic goal (patient-reported thirst) episodes per 100 patient-years.

ESHOL Clinical Trial

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## Facilitating High Convective Doses: Which knobs to turn to achieve HighVolumeHDF?



**Prof. Bernard Canaud**  
Nephrology Department Montpellier University School of  
Medicine, Lapeyronie Hospital, Montpellier, France

Professor Bernard Canaud is currently Professor of Nephrology at the Montpellier University School of Medicine, Lapeyronie Hospital, Montpellier, France and has been since 1990. He was made Head of the Nephrology department in 1998, and since 2002 has also held the position of Head of AIDER (Association pour L'Installation à Domicile des Epurations Rénales), a regional non-profit association for end-stage renal disease patients. Professor Canaud graduated in Medicine from the Montpellier Medical School in 1980 and went on to specialize in Nephrology in 1981. He went on to receive his Master of Science doctorate in Food and Nutrition from the University of Sciences, Montpellier in 1986. Meanwhile, Professor Canaud held the positions of Assistant in Critical Care Medicine from 1981 to 1984 and Assistant Professor of Nephrology from 1984 to 1988 at Montpellier University.

Professor Canaud serves on the Editorial Board of many journals including *Néphrologie & Thérapeutique*, *Journal of Nephrology*, *Blood Purification*, *American Journal of Kidney Diseases*, *Clinical Nephrology*, *Kidney International*, *Journal of the American Society of Nephrology*, *Journal of Vascular Access*, *Hemodialysis International*, *Portuguese Journal of Nephrology and Hypertension* and *Nephrology Dialysis Transplantation*. He is also a member of many scientific societies. He is past president of the *Société Francophone de Dialyse (SFD)*. He is president of the *Association pour l'Installation à Domicile des Epurations Rénales (AIDER)* a non-profit association that cares for chronic kidney patients on renal replacement therapy. He created an institute for dialysis training and research as IRFD "Institut de Recherche et Formation en Dialyse". He contributed to the elaboration and production of the European Best Practice Guidelines particularly on dialysis fluid purity, vascular access, dialysis adequacy and anemia management. He has led the EUDIAL working group dedicated to the improvement of outcome in dialysis dependent patients.

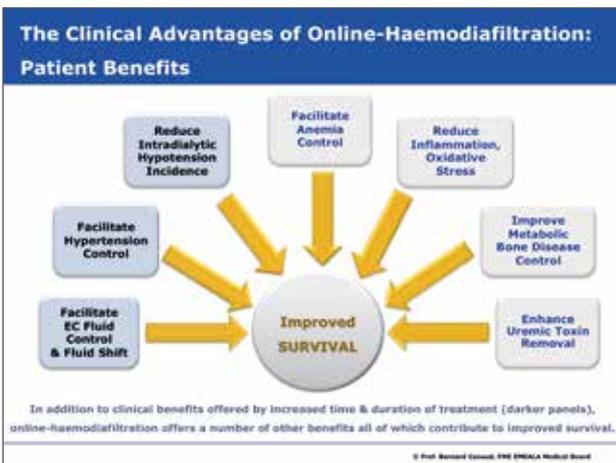
Prof. Canaud joined Fresenius Medical Care in May 2012 as the Chairman of the EMEALA Medical Board.

The effective (or total) ultrafiltered volume, equivalent to the total convective volume, is a surrogate of the **convective dose**, and has been proposed by the EUDIAL initiative as the key quantifier of online-haemodiafiltration in addition to standard adequacy measures. With the **emerging concept** of convection volume impacting patient survival (described by the previous speakers), we examine the factors and practical approaches by which maximal convection volumes can actually be achieved and individualised for each patient treated with online-haemodiafiltration. With these factors in mind, all attempts should be made to maximise convective volume, and hence the convective dose, to enable the patient to derive the full benefits of online-haemodiafiltration over extended periods. It is thus relevant to examine the basic principles involved and the practical clinical approaches by which maximal convection volumes can be achieved for each patient treated with online-haemodiafiltration.

In this presentation, factors governing ultrafiltration, solute convective flux and solute mass removal will be discussed together with the significance of the concepts of blood versus plasma flow as well as filtration fraction: hydraulic permeability, sieving properties of the membrane and surface area of the dialyzer, hydrostatic trans-membrane pressure, blood flow rate (vascular access) are all critical as they have significant direct effects on the targeted ultrafiltration rate and need to be considered together with patient parameters such as haematocrit, protocrit and haemoreological changes.

Finally, based on Prof. Canaud's clinical experiences, the **practical clinical approaches** by which ultrafiltration in HighVolumeHDF can be optimised will be presented. In daily clinical practice achieving this primary target is based on three essential approaches:

1. Patient-dependent factors
2. Prescription (or physician)-dependent factors
3. Technical or machine-dependent factors




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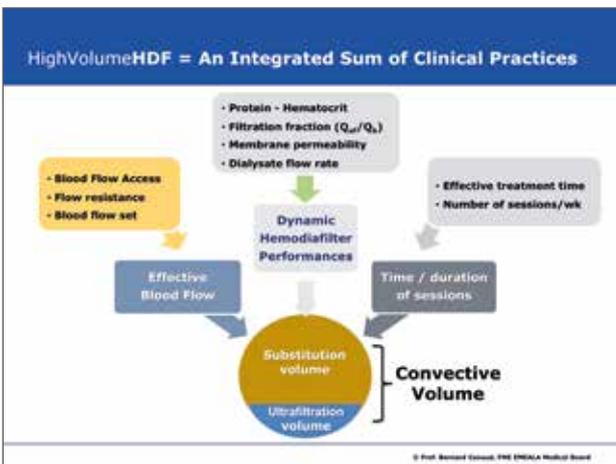
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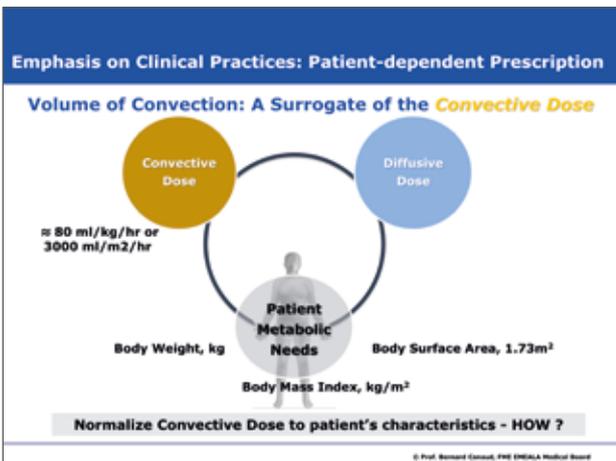
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