



Fig. 1. Suggested flow diagram for reporting of long-term major adverse events after coronary angiography with iodinated contrast in the CARE trial.

revascularization. Perhaps a future report from the CARE trial can inform the reader about these 38 subjects, particularly those who suffered CI-AKI with respect to their courses of treatment and care in the year of follow-up after the trial. By filling in the circles and boxes in Figure 1, the authors could allow inferences on translation of CK-AKI into long-term adverse events and the issue of cause and effect.

Conflict of interest statement. Dr. McCullough is a consultant for GE Healthcare.

References

1. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2008; 51: 1419–1428
2. Solomon RJ, Mehran R, Natarajan MK *et al.* Contrast-induced nephropathy and long-term adverse events: cause and effect? *Clin J Am Soc Nephrol* 2009; 4: 1162–1169
3. Solomon RJ, Natarajan MK, Doucet S *et al.* Investigators of the CARE Study. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation* 2007; 115: 3189–3196

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Optimizing haemodiafiltration: tools, strategy and remaining questions

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Haemodiafiltration (HDF) is considered the best dialysis therapy currently available in terms of optimal removal of both small and middle molecules. This is obtained by combining diffusive and convective clearance. The efficacy of diffusive transport is usually quantified and monitored by the assessment of small molecule clearance. For this purpose, urea clearance expressed as Kt/V_{urea} has been widely accepted and used as a parameter for dialysis adequacy. In contrast, it is currently unclear how the efficacy of convective transport should be quantified and monitored.

Pre-dialysis β_2 -microglobulin (β_2M , 11.8 kD) levels have been accepted as a marker for middle molecules [1]. In two large studies, β_2M levels have been associated with mortality risk, at least within the range as usually found in haemodialysis patients [2,3]. However, the clinical use of β_2M levels to monitor the effects of increased convective clearance by HDF is severely limited by its strong dependence on residual kidney function [4]. To overcome this limitation, the β_2M reduction ratio or Kt/V_{β_2M} could be assessed to measure clearance during HDF, similar to urea. However, in the Hemodialysis (HEMO) study, β_2M clearance did not relate to clinical outcome [2].

Alternatively, convective transport could be quantified by monitoring convective volumes. It has been shown that

Table 1. Factors determining convective volume in post-dilution HDF

Determining factors	Effect on convective volume
Patient related	
Haematocrit ↑	↓
Total protein ↑	↓
Serum albumin ^a ↑	↑
Vascular access	↑↓
Treatment related	
Blood flow rate ↑	↑
Session length ↑	↑
Filtration fraction ^b ↑	↑
Intradialytic weight loss	↑↓
Dialyser characteristics	↑↓

^a The association between albumin and convective volume is the result of opposite factors. High albumin levels may facilitate large convective volumes by enhancing plasma refill rates, thus diminishing blood volume changes during treatment. Alternatively, high albumin levels may compromise convective volumes by increasing the thickness of the protein layer on the dialyser membrane, thereby decreasing the membrane permeability.

^b Maximal tolerable filtration fraction is dependent on transmembrane pressure.

the convective volume is related to the β 2M reduction ratio during a single HDF session [5,6]. Importantly, the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that in order to benefit from HDF in terms of survival, the infusion volume should be at least 15 L per session (i.e. effective convective volume of 17 L per session, assuming an average net ultrafiltration of 2 L per session) [7]. These data suggest a dose and effect relationship between the convective volume and clinical outcome. Current European Guidelines recommend to apply convective volumes as high as possible, with consideration of safety [8]. In practice, these large amounts of infusion fluids should be produced online. Furthermore, post-dilution HDF (infusion occurs post-filter) results in a more effective removal of uraemic toxins than pre-dilution HDF (infusion occurs pre-filter) and is therefore recommended [9,10].

Recently, we have shown that achieved convective volumes were highly variable among patients and centres in a large cohort of HDF patients in a multi-centre setting [11]. The factors determining the convective volume in post-dilution HDF are summarized in Table 1. Modifiable treatment-related factors include obvious ones as treatment time and dialyser blood flow rate. In addition, dialyser characteristics such as surface area, fibre inner diameter, fibre length, pore size and membrane material might be of relevance. As of yet, the role of these characteristics has not been systematically evaluated. In general, it seems wise to choose for a high-flux dialyser with a relatively large surface area. Variations in intradialytic weight loss may influence the convective volume in either direction. A large weight loss *per se* contributes to the convective volume. Moreover, in fluid-overloaded patients, the blood may be diluted at the beginning of treatment, facilitating high filtration rates. Conversely, haemoconcentration by decreased blood volumes at the end of the session may diminish the convective volume.

The relationship between convective volume and dialyser blood flow rate is often referred to as the filtration fraction (i.e. the ratio of convective flow to blood flow). Theoretically, the ratio of convective flow to plasma flow should be used instead to account for individual differences in haematocrit level, but this is not very practical for clinical use. The relationship between treatment time, blood flow rate and filtration fraction on the one hand and on the other hand the convective volume that can be achieved in post-dilution HDF are illustrated in Table 2. It is apparent from this table that the convective volume can be increased with 7.1 L per session (i.e. ~50%) by increasing the filtration fraction from 20 to 30% in a patient treated for 4 h with a blood flow rate of 300 mL/min. Blood flow rates ranging from 300 to 400 mL/min as indicated in Table 2 assume the presence of an adequate vascular access. In our experience, filtration fractions between 25% and 30% are generally feasible when haematocrit levels are kept within the range as advised by current guidelines. When using

Table 2. Convective volumes in post-dilution HDF in relation to treatment time, blood flow rate and filtration fraction

FF (%)	Treatment time = 3 h 00 min													
	20	21	22	23	24	25	26	27	28	29	30	31	32	33
$Q_B = 300$ mL/min	10.8	11.3	11.9	12.4	13.0	13.5	14.0	14.6	15.1	15.7	16.2	16.7	17.3	17.8
$Q_B = 350$ mL/min	12.6	13.2	13.9	14.5	15.1	15.8	16.4	17.0	17.6	18.3	18.9	19.5	20.2	20.8
$Q_B = 400$ mL/min	14.4	15.1	15.8	16.6	17.3	18.0	18.7	19.4	20.2	20.9	21.6	22.3	23.0	23.8
FF (%)	Treatment time = 3 h 30 min													
	20	21	22	23	24	25	26	27	28	29	30	31	32	33
$Q_B = 300$ mL/min	12.6	13.2	13.9	14.5	15.1	15.8	16.4	17.0	17.6	18.3	18.9	19.5	20.2	20.8
$Q_B = 350$ mL/min	14.7	15.4	16.2	16.9	17.6	18.4	19.1	19.9	20.6	21.3	22.1	22.8	23.5	24.3
$Q_B = 400$ mL/min	16.8	17.6	18.5	19.3	20.2	21.0	21.8	22.7	23.5	24.4	25.2	26.0	26.9	27.7
FF (%)	Treatment time = 4 h 00 min													
	20	21	22	23	24	25	26	27	28	29	30	31	32	33
$Q_B = 300$ mL/min	14.5	15.1	15.8	16.6	17.3	18.0	18.7	19.4	20.2	20.9	21.6	22.3	23.0	23.8
$Q_B = 350$ mL/min	16.8	17.6	18.5	19.3	20.2	21.0	21.8	22.7	23.5	24.4	25.2	26.0	26.9	27.7
$Q_B = 400$ mL/min	19.2	20.2	21.1	22.1	23.0	24.0	25.0	25.9	26.9	27.8	28.8	29.8	30.7	31.7

Percentages represent filtration fractions (i.e. convective flow rate divided by blood flow).

Convective volumes >17 L per treatment are indicated in grey.

Values represent convective volumes in litres per treatment.

Q_B = dialyser blood flow, FF = filtration fraction.

relatively large high-flux dialysers, transmembrane pressures (TMP) are usually acceptable.

Based on the above-mentioned considerations and our clinical experience, we suggest the following steps when initiating HDF treatment in the post-dilution mode: (i) ascertain the presence of a vascular access allowing blood flows of at least 300 mL/min, (ii) choose a relatively large dialyser, (iii) set treatment time at 4 h or more, (iv) keep haematocrit levels within the currently recommended range and (v) start with a filtration fraction of 25% and adjust upwards as long as TMP levels are within safe limits. With this strategy, convective volumes of at least 20 L per session will be achieved in most cases.

At present, several uncertainties remain. Firstly, it is questionable whether β_2M is a reliable marker of middle molecules, since levels may be influenced by factors other than kidney and dialyser clearance, for instance by inflammation and residual kidney function. Moreover, it remains to be investigated whether the lowering of β_2M by HDF leads to improved survival. Secondly, the role of β_2M in monitoring middle molecule clearance and therefore convective transport is unclear. In the HEMO study, only pre-dialysis β_2M levels were predictive for mortality in the total cohort, but β_2M clearance was not [2]. Thirdly, modelling suggests that β_2M levels may only slightly decrease when convective volumes are increased in the range as used for post-dilution HDF, which has been explained by the resistance to β_2M transfer between body compartments [12]. This may indicate that favourable effects on pre-dialysis β_2M levels by increasing the convective volume from, for instance, 15–25 L per treatment may be limited. It is therefore very much possible that increasing frequency of treatment sessions is much more effective than improving individual sessions *per se*.

In conclusion, results from DOPPS provide the only data relating convective transport to a meaningful clinical endpoint. This study suggested a survival benefit when infusion fluids were between 15 and 25 L per session (i.e. convective volumes approximately between 17 and 27 L per session). As explained above, the assessment of β_2M as surrogate for convective transport has important drawbacks. Given the increasing interest in online HDF, we considered it appropriate to present a practical set of recommendations that might be helpful for the dialysis staff who wish to optimize treatment with online HDF. With these recommendations, effective convective volumes of 20 L or more will often

be achieved. In order to confirm and detail the observational data provided by DOPPS, properly designed clinical studies relating various levels of convective volume to clinical endpoints seem to be the only appropriate method to define the minimal and/or optimal convective dose.

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References

1. European Best Practice Guidelines for Haemodialysis. II.2 Haemodialysis dose quantification: middle molecules (MM). *Nephrol Dial Transplant* 2002; 17 (Suppl 7): 21–23
2. Cheung AK, Rocco MV, Yan G *et al.* Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study. *J Am Soc Nephrol* 2006; 17: 546–555
3. Okuno S, Ishimura E, Kohno K *et al.* Serum beta-2-microglobulin level is a significant predictor of mortality in maintenance haemodialysis patients. *Nephrol Dial Transplant* 2009; 24: 571–577
4. Fry AC, Singh DK, Chandna SM *et al.* Relative importance of residual renal function and convection in determining beta-2-microglobulin levels in high-flux haemodialysis and on-line haemodiafiltration. *Blood Purif* 2007; 25: 295–302
5. Lin CL, Yang CW, Chiang CC *et al.* Long-term on-line hemodiafiltration reduces predialysis beta-2-microglobulin levels in chronic hemodialysis patients. *Blood Purif* 2001; 19: 301–307
6. Lornoy W, Becaus I, Billioux JM *et al.* On-line haemodiafiltration. Remarkable removal of beta-2-microglobulin. Long-term clinical observations. *Nephrol Dial Transplant* 2000; 15: 49–54
7. Canaud B, Bragg-Gresham JL, Marshall MR *et al.* Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int* 2006; 69: 2087–2093
8. Tattersall J, Martin-Malo A, Pedrini L *et al.* EBPG guideline on dialysis strategies. *Nephrol Dial Transplant* 2007; 22: ii5–ii21
9. Ahrenholz P, Winkler RE, Ramlow W *et al.* On-line hemodiafiltration with pre- and postdilution: a comparison of efficacy. *Int J Artif Organs* 1997; 20: 81–90
10. Meert N, Eloit S, Waterloos MA *et al.* Effective removal of protein-bound uraemic solutes by different convective strategies: a prospective trial. *Nephrol Dial Transplant* 2009; 24: 562–570
11. Penne EL, van der Weerd NC, Bots ML *et al.* Patient- and treatment-related determinants of convective volume in post-dilution hemodiafiltration in clinical practice. *Nephrol Dial Transplant* 2009; 24: 3493–3499
12. Ward RA, Greene T, Hartmann B *et al.* Resistance to inter-compartmental mass transfer limits beta-2-microglobulin removal by post-dilution hemodiafiltration. *Kidney Int* 2006; 69: 1431–1437

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