Moreover, the impact of frequent HD regimens raises concerns, especially regarding vascular access (VA) complications, either VA interventions [5] or infections [6]. Another potential harmful effect of frequent HD regimens is the more rapid development of anuria [7].

In addition, frequent HD also considerably increases the burden for patients and their caregivers, in terms of time, logistics and costs, especially with in-center frequent schedules.

Having in mind the uncertain impact of frequent HD schedules on survival, their potential harmful effects and the associated increased costs and burden, we recommend, before increasing HD frequency, a number of underused strategies improving patient tolerance and/or HD dose, as detailed in our paper. Although there is no documented evidence that alternate-day regimens improve survival, it might be an attractive option for selected patients after all other available options have failed. However, these regimens will definitely prove difficult to implement widely in most HD facilities.

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Longer or more frequent HD regimens, considered as more physiological in terms of solute removal and haemodynamic stability, have thus been proposed in order to improve survival and other important patient outcomes. Frequent HD regimens include short daily HD (SDHD): 5–7 weekly 1.5–3 h; nocturnal HD (NHD): 5–7 weekly 6–8 h or alternate day schedules: ~4 h every other day.

Still, very few randomized controlled trials (RCTs) focusing on frequent HD therapies have been published [1–4]. Overall, some benefits of the more frequent HD schedules have been well documented, i.e. an improvement in blood pressure (BP) control [1, 2, 5–7], a reduction in left ventricular mass (LVM) [1, 3, 5], lower ultrafiltration rates [8] and a better control of phosphataemia [1–3, 9], especially in patients receiving NHD. Additionally, these regimens avoid the long interdialytic interval, which has been associated with an increased risk of death and hospital admission for cardiovascular events, both in US and non-US populations [10, 11]. These results suggest that larger weight gains and higher K levels at the end of the long HD interval, triggering higher ultrafiltration rates and more rapid K decrease, may lead to death.

Whether these well-documented benefits, and other potential advantages, provide a sufficient rationale for the generalized prescription of frequent HD schedules is, however, highly debatable or unfounded. Indeed, as summarized below, the impact of frequent HD regimens on a number of important outcomes remains uncertain, or can even be detrimental for some outcomes.

**Survival: Inconclusive Results from RCTs and Potential Pitfalls of Retrospective Cohort Studies**

The impact of frequent HD schedules on survival has been investigated in only two RCTs: the Frequent Hemodialysis Network (FHN) Daily Trial, comparing the effects of in-centre SDHD (1.5–2.75 h/session, six sessions per week) with conventional thrice-weekly (CHD) in-centre HD (total n = 245) [1], and the FHN Nocturnal Trial, comparing frequent home NHD (six times per week for ≥6–8 h per session) with CHD home HD (total n = 86) [2]. In both trials, survival was part of two co-primary composite outcomes (death or 12-month change in LVM and, separately, death or 12-month change in the physical health composite score). In the Daily Trial, both composite end points were met with SDHD, but this was driven by the (modest) LVM regression and better self-reported physical scores rather than by reduced mortality [1], despite a 23% increase in mean total weekly dialysis time and thus higher total K/\(V_{urea}\). The authors rightly did not allow participants to perform SDHD at home to avoid a HD setting bias. Unfortunately, this trial presented several other limitations. First, there were few deaths in each arm (five and nine patients in the SDHD and CHD groups, respectively, total mortality 7.5%), probably unsurprisingly over only 52 weeks with such a moderate sample size (n = 245) due to slow recruitment (<4% of the 6000 screened patients accepted to participate). Thus, the study was admittedly relatively underpowered to detect a difference in survival. Secondly, 22% of the patients in the frequent HD arm attended <80% of the sessions (versus 5.1% in the CHD arm), a sign of the burden of this intensive regimen. The Nocturnal Trial included even fewer patients (n = 87) as recruitment was even more difficult, and did not detect an effect of frequent NHD on either of the two co-primary outcomes, and was, again, significantly underpowered [2].

Retrospective registry studies have mostly shown a lower mortality risk with both SDHD and NHD regimens, irrespective of the number of weekly sessions (reviewed in [12, 13]). Of note, frequent HD schedules are performed at home in most studies, strongly suggesting a setting selection bias, with more autonomous and educated patients dialysing at home. Other factors that may also account for the observed ‘survival advantage’ include a greater delivered dose of HD, longer duration of each HD session and bias by indication (prescription of frequent HD regimens to patients with an underlying indication for longer or more frequent sessions, such as higher interdialytic weight gain).

Importantly, in a large Australian study attempting to eliminate the confounding effect of HD settings, Marshall et al. [14] observed no difference in mortality rates, neither between frequent/extended home schedules and thrice weekly home HD, nor between frequent/extended in-centre HD and thrice-weekly in-centre HD. Survival was better in home regimens, suggesting thus a greater impact of HD settings than HD frequency. Moreover, a recent multinational cohort study including 318 patients receiving in-centre SDHD (≥6 weekly sessions, weekly HD time 15.7 h) and 575 propensity-score matched patients from the Dialysis Outcomes and Practice Patterns Study, followed for 18 months, surprisingly documented an increased mortality in the SDHD arm (HR 1.6; \(P = 0.023\)) [15]. Admittedly, there was no information about adherence to the HD prescription or the reason for the prescription of daily HD, and most included HD patients were prevalent. Nevertheless, the study design eliminated the confounding effect of differences in HD settings (both groups received in-centre HD), and added thus uncertainty concerning the real impact of frequent HD regimens on survival.

Overall, the evidence to recommend widespread adoption of frequent HD regimens based on survival data is nowadays grossly inadequate: the two published RCTs are inconclusive, and retrospective cohort studies present numerous biases and show conflicting results, especially after eliminating the confounding effect of dialysis setting (in-centre versus home).

**The Impact of Frequent HD Regimens Raises Concerns**

**Vascular access**

Small, old studies have shown similar or even improved vascular access (VA) survival with daily HD regimens. However, the time to the first VA event (VA intervention, VA loss or VA-related hospitalization) was shorter (HR 1.7; \(P = 0.02\)) in patients assigned to in-centre SDHD in a subanalysis of the Daily FHN, compared with patients receiving CHD.
[16]. Although not significant, a trend towards an increase in the number of VA interventions and the time to first VA event was also observed in the Nocturnal FHN Trial ($P = 0.095$ and $0.07$, respectively) [16]. The authors hypothesized that higher rates of VA complications in the frequent HD arm could be explained by increased surveillance by nursing staff [1]. However, thrombectomies and surgical revisions accounted for 55% of VA interventions, thus pointing to thrombosis as the main VA event, a finding unlikely to result from more intensive surveillance [17]. A more plausible explanation is the more frequent mechanical trauma from VA cannulation, and/or repeated compression of cannulation sites after HD [17]. Unfortunately, the available information regarding VA was restricted to VA type and did not include important data such as VA vintage, infectious complications or cannulation technique. Finally, although both FHN trials suggest that frequent HD may increase complications rates for both arterious-venous fistulas (AVF) and arterious-venous grafts, with some differences between SDHD and NHD, they do not support any preference or avoidance of one type of VA. Interestingly, in a recent Australian observational study including 286 patients (>90% with an AVF) dialysed predominantly at home, the risk of VA events (60% of whom were infections) was independently predicted only by dialysis frequency [HR per 1-session increase 1.56 (1.03–2.36); $P = 0.04$] [18].

Overall, despite the above-mentioned limitations, the data support an association of VA complications (mechanical and infectious) with frequent HD therapies.

**Residual renal function**

In a post hoc analysis of the FHN trials, frequent NHD was associated with a higher percentage of newly anuric patients than CHD (52 versus 18%, $P = 0.015$; 67 versus 36%, $P = 0.06$ at 4 and 12 months, respectively). Moreover, the onset of anuria was correlated with the number of weekly HD sessions [19]. In contrast, residual renal function (RRF) loss was similar in SDHD and CHD patients in the daily FHN trial. The proposed causes of this accelerated loss of RRF in NHD include differences in volume status, discontinuation of angiotensin converting enzyme inhibitors and angiotensin receptor blockers, reduced solute load leading to a reduction in plasma volume and biocompatibility issues. As pointed out by Farrington [20], an additional factor could be the greater exposure to radiographic contrast agents due to VA procedures in the NHD group. Admittedly, this analysis was potentially biased by differences in urine collection methods (leading to underestimation of RRF in frequent HD groups) and by the difference in the inclusion criteria between cohorts (RRF being much lower in the Daily than in the Nocturnal FHN trial, potentially thus preventing the detection of an impact of daily schedules on RRF). Nonetheless, the practitioner should consider this potential harmful effect of frequent HD regimens on RRF in order to target the patients most likely to benefit from these more intensive therapies.

**Perceived burden and adherence issues**

Frequent HD therapies are associated with a considerable increase in logistical requirements (cost and time of transportation to the HD unit, and social support) and in time requirements (learning process, repeated preparation and cleaning of the HD machine, repeated cannulation for home-based treatments), for patients and caregivers. Using a 10-question Cousineau scale of perceived burden, Suri et al. [21] found that in-centre SDHD did not result in higher perceptions of burden on caregivers in the Daily FHN trial. In contrast, there was a trend towards higher perceived burden among patients receiving NHD ($P = 0.08$). As perception by patients of a greater burden on their caregivers could result in therapy refusal, switching modality rate and patient adherence to prescribed regimens could be used as estimates of perceived burden. The switching rate was consistently higher among patients receiving frequent HD therapies (daily or nocturnal) than in those on CHD in three registry studies (reviewed in [12]). Of note, patients adherence was also significantly lower in both FHN trials in patients randomized to frequent therapies ($P < 0.001$ in both trials) than in patients on CHD regimens [1, 2]. In conclusion, the clinician should consider these data, which are likely to affect long-term adherence, especially to nocturnal regimens.

**Economics**

Some economic evaluations using primarily in-centre HD patients as the comparator (the most resource-intensive dialysis modality) have reported that both conventional and even more frequent home-based HD are less costly than conventional in-centre HD. A recent standardized costing model, based on data from Australia, Canada and the UK, compared costs for conventional home HD, frequent home HD and conventional in-centre HD, from the payers’ perspective [22]. Overall, the analysis showed significant differences in the ranking of the cost of these three modalities both between countries and between the first year and subsequent years. In a recent Canadian cost-utility analysis, frequent home NHD was attractive compared with in-centre CHD [23].

Overall, from the payers’ perspective, awaiting the cost analysis of the US Daily FHN Trial, it appears very likely that the high cost of individual HD sessions, still paid on a fee for
service basis rather than as a bundle in most countries, would completely preclude the more generalized use of frequent in-centre HD, in the current cost-containment era typical of all Western healthcare systems. Needless to say that, in a bundle environment, the higher cost of more frequent in-centre schedules would be transferred to providers rather than avoided.

**Areas of Uncertainty**

**Quality of life**

Prospective cohort studies have almost consistently reported improved quality of life (QOL) with SDHD or NHD [12]. However, once again, the results of RCT are less optimistic. The Daily FHN trial documented a significant improvement in the self-reported physical health scores [1] and mental health and emotional subscale scores [24] with in-centre SDHD compared with CHD, without differences in depression scores. In contrast, the Nocturnal FHN trial showed no difference [24]. Moreover, a third RCT comparing frequent (six times weekly) NHD and CHD in 52 patients also failed to show a difference in patient QOL (P = 0.43) [3].

**Hospitalizations unrelated to VA**

Despite the proven benefits of frequent HD therapies on BP control, LVH and phosphate homeostasis, the published literature remains inconclusive concerning hospitalization rates [1, 2, 25].

**Anaemia**

No differences in anaemia control or use of erythropoiesis-stimulating agents were observed in the three RCTs in SDHD [1] or in NHD [2, 3] analysing this outcome. Results of observational studies are conflicting.

**Nutritional parameters**

Preliminary data have suggested a beneficial effect on nutrition parameters with frequent HD therapies [26]. However, in-centre SDHD reduced extracellular water, but did not increase serum albumin levels or equilibrated protein catabolic rate in comparison with CHD in the Daily FHN trial. Frequent home NHD had no impact on any nutritional or body composition parameter [27]. A recent review of short-term studies (three SDHD and five frequent NHD trials) failed to show any improvement in serum albumin levels, weight, protein catabolic rate, or protein or energy intake [28].

**Summary and Conclusions**

Overall, any benefits of more frequent HD regimens definitely need to be balanced against potential harmful effects on VA, RRF and patient adherence to the prescribed therapy (Table 1). In addition, the available data show that the impact of frequent therapies on survival is, at best, inconclusive and, at worse, harmful. Frequent HD also considerably increases the burden for patients and their caregivers, logistics and costs, especially with in-centre frequent schedules. Importantly, the clinician should keep in mind that, before increasing HD frequency, a number of underused strategies improving patient tolerance and/or HD dose should be tested first:

(i) Optimization of BP control in hypertensive patients with conservative measures: progressive target weight reduction, dietary sodium and fluid restriction, dialysate sodium tailoring to serum sodium and adaptation of antihypertensive medications [4].

(ii) Increasing the duration of the thrice-weekly sessions, in order to improve haemodynamic tolerance, (especially in patients with severe cardiac disease) and middle molecule clearance.

(iii) Addition of a convective gradient (haemodiafiltration).

(iv) Alternate day HD eliminates that the long interdialytic interval and is perhaps less likely to be associated with VA complications than more frequent HD schedules. It might be thus an attractive option when the above detailed measures have failed. Many of our home HD patients are currently dialysed on an alternate day basis, with the obvious advantage of avoiding the long, sometimes risky long interval. Whether alternate day schedules would be feasible and beneficial in the in-centre setting is yet, however, unclear.

Awaiting definitive large-scale studies, the potential benefits and risks of each HD modality should be taken into account for each individual patient after consideration of comorbidities, age, RRF, anticipated duration of dialysis therapy and life expectancy. Last but not least, the unacceptably high societal costs and burden of frequent HD programmes, especially in-centre (the most common setting of HD worldwide), make the generalization of such regimens unwarranted. Frequent HD schedules should be reserved for selected cases, only after the other available options have failed.

**Conflict of Interest Statement**

None declared.

(See related article by Zoccali et al. Should we extend the application of more frequent dialysis schedules? A ‘yes’ and a hopeful ‘no’. Nephrol Dial Transplant 2015; 30: 29–32; See related article by Georgianos and Sarafidis. Pro: Should we move to more frequent haemodialysis schedules? Nephrol Dial Transplant 2015; 30: 18–22.)

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Labriola et al. [1] support that available randomized studies show no clear survival benefit of short daily haemodialysis (SDHD) or frequent nocturnal haemodialysis (NHD). In the Frequent Hemodialysis Network (FHN) trial [2], mortality was not a prespecified separate primary end point; thus, it was clear from the start that the study was underpowered to detect a difference in mortality alone. In this case, the proper comment seems to be that ‘absence of evidence does not mean evidence of absence of effect’. The FHN trial demonstrated among other a significantly greater regression in the left ventricular mass in favour of SDHD; at least this effect cannot be neglected, as it clearly affects survival in haemodialysis patients [3].

With regard to observational studies, improved survival of 15–45% with enhanced-frequency dialysis (i.e. home NHD) was previously noted in several studies [4, 5]. We agree with Labriola et al. [1] that this outcome could be influenced by selection bias, higher dialysis dose, setting and other factors.