Port J Nephrol Hypert 2016; 30(2): 102-103 • Advance Access publication 17 May 2016

Too Much Medicine
Dialysis time and survival: Pursuing fashionable trends of dubious importance?

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The prestigious *Journal of the American Medical Association* published a study in 2000 by Barbara Starfield which revealed the extremely poor performance of the United States health care system when compared to that of other industrialised nations. According to this study, prescription drugs are the third most common cause of death in the US, after heart disease and cancer[1].

One of the major causes of overtreatment certainly has to do with the commercial interests of the pharmaceutical industry. The last few years have seen the majority of the largest pharmaceutical companies paying considerable fines in the US for various misconducts, including hiding data on harms, and the misrepresentation of research results.

According to Richard Horton, editor of the *Lancet*, "the case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue. Afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable trends of dubious importance, science has taken a turn towards darkness"[2]. A scientific literature that is frequently untrue will obviously induce too much medicine.

There is in general a lack of good quality evidence shaping haemodialysis practice patterns, and thus what constitutes adequate dialysis remains difficult to ascertain and is for the most part opinion-based. In fact, there is only limited evidence on the clinical outcomes of different interventions, as is the case for longer and shorter dialysis session lengths.

Yet, dialysis time is increasingly being used as a quality measure. In many European countries Clinical Practice Guidelines recommend that patients be dialysed for longer than 4 hours, and large dialysis providers worldwide have developed a performance measure leading physicians to prescribe a minimum dialysis session length as a quality target, typically, a weekly treatment time equal to or greater than 720 minutes.

Most often, the Key Performance Indicator (KPI) has been the *weekly treatment time≥720 minutes,* requiring that a certain percentage of patients be dialysed longer than 4 hours per session. The evidence supporting this KPI came mainly from two recently published observational studies [3,4] that found an increased risk of mortality in patients with an observed session length <240 minutes as compared with those with a session length ≥240 minutes. However, these studies have been assessed by Daugirdas, who found several potential concerns with them, including lack of internal consistency, biologic implausibility, and increased risk of dose-targeting bias[5]. According to Daugirdas, "the results of these studies suggest a regulatory or quality bias active at the 240-minute time point rather than a biologic adverse effect of slightly shorter treatment times".

Unfortunately, the potential benefits of longer dialysis times have only been assessed in observational studies[3,4,6,7-12]. However, using the GRADE framework, evidence from observational studies is rated as low in quality. Applying the GRADE methodology to this body of evidence composed of a set of observational studies (some examples can be found at the end of this article: references 3, 4, 6, 7-12), would rate the quality of those studies as low (as none of the reasons suggested by GRADE for rating up the quality of evidence is present), meaning that "our confidence in the estimates of effect is limited, and that the true effect may be substantially different from the estimate of effect"[13,14].

It is important to note that these observational studies (references 3, 4, 6, 7-12) have a high risk of bias resulting

from confounding by indication, as patients prescribed a longer dialysis session length are possibly healthier overall (a lower dialysis session length is usually prescribed to sicker patients). This hypothesis has been confirmed by at least three of those studies[7-9]. Furthermore, the categorisation of dialysis session length into several distinct groups as a *post hoc* analysis largely inflates the risk of type I error (meaning rejecting the null hypothesis when the null hypothesis is true). Noteworthy, these studies have shown inconsistent results, with some studies showing improved survival with dialysis session length longer than 4 hours, while in others longer dialysis time has shown no benefit or was even associated with decreased survival[3,4,7,10-12].

Furthermore, the benefit of longer haemodialysis session length, shown by some observational studies but not by others, is not consistent with randomised trials either. For example, in the HEMO trial[14], dialysis session length was an integral part of the dose intervention, as the target dialysis dose could not be achieved simply by changes in size of dialyser membrane. Accordingly, in patients allocated to the high-dose group, dialysis session length was 219 minutes, while in those allocated to the standard-dose group, dialysis session length was 190 minutes, a 30-minute difference. Yet, no difference in mortality was observed.

Longer dialysis session length increases the burden of the disease on patients. When selecting quality measures, leaders of the performance-measurement process tend to ignore the issues of the burden imposed on patients, as well as patients' preferences.

Currently, there is insufficient evidence to support the inclusion of criteria related to dialysis time in definitions of adequate haemodialysis practice. Longer dialysis session length is an intervention of unproven value, and, therefore, dialysis time should not be used as a KPI or as a quality measure. Further, with the available data, using dialysis time as a performance measure should be considered a clear example of overtreatment.

References

1. Starfield B. Is US health really the best in the world? *JAMA.* 2000; 284(4):483-485
2. Horton R. Offline: What is medicine's 5 sigma? The Lancet 2015; 385:1380
3. Flythe JE, Curhan GC,Brunelli SM. Disentangling the ultrafiltration rate-mortality association: the respective roles of session length and weight gain. Clin J Am Soc Nephrol 2013; 8:1151-1161
4. Brunelli SM, Chertow GM, Ankers ED, Lowrie EG, Thadhani R. Shorter dialysis times are associated with higher mortality among incident dialysis patients. Kidney Int 2010; 77:630-636
5. Daugirdas JT. Dialysis time, survival, and dose-targeting bias. Kidney Int 2012; 83: 9-13
6. Marshall MR, Byrne BG, Kerr PG, McDonald SP. Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients. Kidney Int 2006;69:1229-1236
7. Miller JE, Kovesdy CP, Nissenson AR et al. Association of hemodialysis treatment time and dose with mortality and the role of race and sex. Am J Kidney Dis 2010; 55(1): 100-112
8. Saran R, Bragg-Gresham JL, Levin NW et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int 2006; 69: 1222-1228
9. Tentori F, Zhang J , Li Y et al. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Ptterns Study (DOPPS). Nephrol Dial Transplant 2012; 27(11):4180-4188
10. Held PJ, Levin NW, Bovbjerg RR, Pauly MV, Diamond LH. Mortality and duration of hemodialysis treatment. JAMA 1991;265: 871-875
11. Lowrie EG, Li Z, Ofsthun N, Lazarus JM. Measurement of dialyzer clearance, dialysis time, and body size: death risk relationships among patients. Kidney Int 2004;66: 2077-2084
12. Ramirez SPB, Kapke A, Port FK et al. Dialysis dose scaled to body surface area and size-adjusted, sex-specific, patient mortality. Clin J Am Soc Nephrol 2012; 7:1977-1987
13. Balshem H, Helfand M, Schünemann HJ et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64: 401-406
14. Guyatt GH, Oxmanc AD, Sultan S et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011; 64: 1311-1316
15. Eknoyan G, Beck GJ, Cheung AK et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002; 347: 2010-2019