Supplement 6| Summary Evidence Tables

Key question 1.1.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Cooper (2010)	RCT	828	Early (403)	Late (424)	Planned early initiation of dialysis in patients with stage V chronic kidney disease was not associated with an improvement in survival or clinical outcomes.
2	Collins (2011)	Subanalysis of the IDEAL trial	362	Early (171)	Late (191)	Patients commencing dialysis early with stage 5 CKD for whom the planned dialysis modality was HD did not have an improvement in survival or any reduction in most clinical outcomes apart from fluid and electrolyte events.
3	Harris (2011)	Subanalysis of the IDEAL trial	642	Early (307)	Late (335)	Planned early initiation of dialysis therapy in patients with progressive chronic kidney disease has higher dialysis costs and is not associated with improved quality of life.
4	Whalley (2013)	Subanalysis of the IDEAL trial	182	Early (91)	Late (91)	Planned early initiation of dialysis therapy did not result in differences in any echocardiographic variables of cardiac structure and function.
5	Korevaar (2001)	Cohort	253	Timely (159)	Late (94)	We conclude that an earlier start of chronic dialysis in patients with end-stage renal disease than currently applied in the Netherlands, and probably in other more developed countries, is not warranted.
6	Traynor (2002)	Cohort	235	Early (119)	Late (116)	Our data do not show any survival advantage from earlier initiation of dialysis for ESRD.
7	Kazmi (2005)	Cohort	302,287			Patients initiating dialysis therapy at greater GFRs have an increased risk for death not fully explained by comorbidity.
8	Hwang (2010)	Cohort	23,551			Lower eGFR at dialysis initiation is associated with lower mortality.
9	Lassalle (2010)	Cohort	11,685			We found that age and patient condition strongly determine the decision to start dialysis and may explain most of the inverse association between eGFR and survival.

10	Wright (2010)	Cohort	801,685			Late initiation of dialysis is associated with a reduced risk of mortality, arguing against aggressive early dialysis initiation based primarily on eGFR alone.
11	Clark (2011)	Cohort	25,910	Early (8,441)	Late (17,469)	A higher glomerular filtration rate at initiation of dialysis is associated with an increased risk of death that is not fully explained by differences in baseline characteristics.
12	Chang (2012)	Cohort	450	Early (225)	Late (225)	Early-start groups had no survival benefit in our study when using a PS approach.
13	Zhang (2018)	Cohort	294	Early (118)	Late (176)	Stratified analyses confirmed elevated eGFR that had no advantage on long-term prognosis.

CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HD, hemodialysis; IDEAL, The Initiating Dialysis Early and Late study; RCT, randomized controlled trial

Key question 1.2.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Kim (2020)	Cohort	1,461	AVF (314)	AVG, CVC (1147)	The patients with AVF had better survival rate and low hospitalization rate, and the patients with AVF or AVG showed both higher HRQOL and lower depression scores than those with CVC.
2	Ozeki (2017)	Cohort	1,341	AVF (975)	AVG, CAVF, CVAVG (366)	The research proved that the survival rate among patients in whom HD was initiated with AVF was significantly higher than that in patients in whom HD was initiated with AVG or CVC.
3	Arhuidese (2019)	Cohort	798,264	AVF (303,273)	AVG (78,340), catheter persistence (416,651)	Female gender is associated with a lower prevalence of preemptive AVF's, higher utilization of catheters as a bridge to AVF, and lower patency compared with males. There was no difference in access maturation but patient survival was higher for females compared with males.
4	Bae (2018)	Cohort	529	Radiocephalic AVF (264), brachicephalic AVF (168)	AVG (97)	Radiocephalic AVF was significantly superior to AVG in terms of vascular access abandonment ($P = 0.005$) and all-cause mortality ($P < 0.001$) in spite of a higher probability of MF. Brachiocephalic AVF was associated with a shorter time to the first needling and fewer interventions before maturation than radiocephalic AVF. Autologous AVF was

						suggested as the preferred VA choice in terms of long-term outcomes in elderly patients.
5	Saleh (2017)	Cohort	46,786	AVF (8,940)	AVG (1,090), tunneled catheter with a maturing AVF or AVG (8,262), tunneled catheter without a maturing AVF or AVG (28,494)	In elderly patients initiating HD with a catheter, the optimal vascular access selection depends on tradeoffs between shorter catheter dependence and less frequent interventions to make the vascular access (AVG) functional versus longer access patency and fewer interventions after successful use of the vascular access (AVF).
6	Shechter (2014)	MonteCarlo simulation	N/A	N/A	N/A	In general, AVF referral within about 12 months of the estimated time to dialysis performed best among time frame strategies, and referral at eGFR <15-20 mL/min/1.73m^2 performed best among threshold strategies. The timing of referral should also be guided by the individual rate of CKD progression. Elderly patients with CKD could be referred later to reduce the risk of creating an AVF that is never used.

AVF, arteriovenous fistula; AVG, arteriovenous graft; CKD, chronic kidney disease; CVC, central venous catheter; CVAVG, initially central venous catheter placement, then transition to arteriovenous graft; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HRQOL, health-related quality of life; N/A, non-applicable

Key question 2.1.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Lowrie (1981)	RCT	151	3 hours (III (41): 3 hours and BUN 50, IV (37): 3 hours and BUN 100)	4.5 hours (I (41): 4.5 hours and BUN 50; II (32): 4.5 hours and BUN 100)	Four treatment groups were divided along two dimensions: dialysis treatment time (long or short), and blood urea nitrogen (BUN) concentration averaged with respect to time (TACurea) (high or low). Dietary protein was not restricted. There was no difference in mortality between the groups. Hospitalization was also greater in the

						high-BUN groups, but dialysis treatment time had no significant effects. The data indicate that the occurrence of morbid events is affected by the dialysis prescription.
2	Dember (2019)	RCT	7,035	3.5 hours (210 minutes) in usual care facilities.	≥4.25 hours (255 minutes)	Although a highly pragmatic design allowed efficient enrollment, data acquisition, and monitoring, intervention uptake was insufficient to determine whether longer hemodialysis sessions improve outcomes.
3	Tentori (2012)	Cohort	37,414	Treatment time (TT): 180 min (8411), 210 min (7,282)	Treatment time (TT): 240 min (16795), 270-300 min (4926)	(DOPPS)Accounting for country effects, mortality risk was lower for patients with longer TT (HR for every 30 min: all-cause mortality 0.94, 95% CI 0.92–0.97], cardiovascular mortality 0.95, 95% CI 0.91–0.98) and sudden death 0.93, 95% CI 0.88–0.98).
4	Flythe (2013)	Cohort	10,571	<240 min (2,382)	≥240 min (2,382)	Compared to prescribed longer dialysis sessions, session lengths less than 240 minutes were significantly associated with increased all-cause mortality adjusted HR 1.26, 95% CI 1.07–1.48, *P* = 0.005)
5	Brunelli (2010)	Cohort	71,746	Shorter session length (<240 min) (4,779)	≥240 min (3,773)	On primary marginal structural analysis, session lengths <4 hours were associated with a 42% increase in mortality.
6	Shinzato (1997)	Cohort	8,553	<4 hours	>4hours, 4-4.5 hours	Figure 2 shows the adjusted RR of death for patient groups with different duration of HD sessions, when a duration 4.0–4.5 hours was taken as the reference range. A progressive decrease in the probability of the death was seen as the HD sessions increased, at least up to 5 hours. 4-4.5 hours(ref), 3.5-4 hours RR 1.68, 3-3.5 hours RR 4.10, <3 hours RR 3.94, 4.5-5.0 hours RR 0.77.
7	Lin (2018)	Cohort	183	Twice-weekly HD (38)	Thrice weekly HD (68)	The similar survival between twice weekly HD and thrice-weekly HD in patients with long-term dialysis vintage is likely relating to patient selection, individualized treatment for dialysis patients based on clinical features and socioeconomic factors remain a tough task for the clinicians.
8	Sun (2018)	Cohort.	107	Twice-weekly HD (126)	Thrice weekly HD (57)	Patients who underwent twice-weekly HD had 4.26 times less chance of survival as compared to patients with thrice-weekly hemodialysis (HR 4.2, *P* = 0.043).
9	Whang (2016)	Cohort.	685	Twice-weekly HD (113)	Thrice weekly HD (137)	Patients with RKF undergoing twice-weekly HD showed an independent association with a greater risk of mortality compared with patients with RKF undergoing thrice weekly HD (HR 4.20, 95% CI 1.02–17.32, *P* = 0.04).

BUN, blood urea nitrogen; CI, confidence interval; DOPPS, Dialysis Outcomes and Practice Patterns Study; HD, hemodialysis; HR, hazard ratio; ref, reference; RR, Relative risk; TACurea, time-averaged concentration of urea; TT, treatment time; RKF, residual kidney function

Key question 2.2.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Eknoyan (2002)	RCT	1,846	High (920)	Standard (926)	The effects of the dose and flux interventions were similar at both levels of the other variable (*P* for interaction=0.30).
2	Held (1996)	Cohort	2,311	Kt/V 1.17-1.32 (462), Kt/V >.33 (462), Kt/V 0.91-1.05 (462), Kt/V <0.91 (463)	Kt/V 1.06-1.16 (462)	0.1 higher Kt/V is associated with a 7% lower mortality risk (RR = 0.93, *P* = 0.01)
3	Bloembergen (1996)	Cohort	2,479	Kt/V 1.2	Kt/V 0.9	All-cause mortality risk was 8% lower (RR = 0.92, *P* < 0.001) for each 0.1 higher Kt/V
4	Shinzato (1996)	Cohort	56,431	Kt/V>1.2 or <1.0	Kt/V 1.0~1.2	A progressive decrease in the probability of death was seen as Kt/V increased until it reached 1.8.
5	Chertow (1999)	Cohort	3,009	Kt <40 or >44.8	Kt 40.0-44.8	Using the third quintile of Kt as the referent category, the RR of death declined with increasing Kt: 1.34 (0.99 to 1.81), 1.06 (0.76 to 1.45), 1.00, 1.00 (0.72 to 1.38), and 0.83 (0.59 to 1.16).
6	Wolfe (2000)	Cohort	9,165			The results are shown as the solid lines in Fig 1, and the negative gradient shows that the mortality rate tends to be less for patients receiving greater Kt/V in each group of patients.
7	Port (2002)	Cohort	45,967	URR >75%	URR 65-70%	The URR 75% group showed a 14% lower mortality risk compared with the 70 to 75% group (RR, 0.86; *P* = 0.0001).
8	Salahudeen (2003)	Cohort	1,151	spKt/V <1.23 or >1.39 (921)	spKt/V 1.23-1.39 (230)	In the multivariate analysis, that is in the presence of all the above variables, the spKt/V -1.2 (under dialysis) persisted as a significant risk factor (2.27, 95% CI 1.42–3.60, *P* = 0.001).
9	Termorshuizen (2004)	Cohort	740	Weekly spKt/V <3.37	Weekly spKt/V >3.37	Among anuric patients, a consistent decrease in mortality with higher levels of dKt/Vurea was found (overall *P* = 0.0008). The mortality figures associated with the three lowest dKt/Vurea quintiles (dKt/Vurea = 2.90/wk) were significantly higher than the mortality figure for the highest quintile (dKt/Vurea = 3.37/wk).
10	Port (2004)	Cohort	10,816	URR >75%	URR 70-75%	For both men and women, patients with a URR less than 60% have significantly greater mortality risk than those in the 65 to 70% category (*P* = 0.0001 for both). Among women, RR for mortality

						declined significantly with increasing eKt/V greater than 1.05 (6% lower per 0.1 higher eKt/V; *P* = 0.001). Among men, RR for mortality did not change significantly with increasing eKt/V (2% lower per 0.1 higher eKt/V; *P* = 0.23).
11	Ramirez (2012)	Cohort	7,229	Male spKt/V >quintile 2, Women	Male spKt/V quintile 1	For spKt/V, the adjusted mortality hazard ratio decreased as spKt/V increased until a dose of approximately 1.6–1.7 was reached.
12	Hong (2019)	Cohort	18,242	spKt/V <1.2 or >1.4	spKt/V 1.2-1.4	Cox regression analyses showed that, compared to the reference (spKt/V 1.2 to <1.4), lower and higher baseline spKt/V values were associated with greater and lesser risks for all-cause mortality, respectively; the case mix-adjusted HRs and 95% CIs were 1.33 (1.19–1.49), 1.09 (1.00–1.19), 0.93 (0.86–1.01), 0.86 (0.78–0.95), and 0.86 (0.77–0.96) for spKt/V values <1.0, 1.0 to <1.2, 1.4 to <1.6, 1.6 to <1.8, and ≥1.8, respectively.

CI, confidence interval; dKT/Vurea, delivered Kt/V of urea; eKT/V, equilibrated Kt/V; HRs, hazard ratios; spKT/V, single-pool KT/V; URR, urea reduction ratio; wk, week

Key question 3.1.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Eknoyan (2002), [HEMO Study]	RCT	1,846	921	925	There was no significant effect of high- versus low-flux membranes on mortality. However, high flux was associated with a significant reduction in several secondary outcomes, including cardiac mortality and a composite outcome of cardiac hospitalization or cardiac death. Patients treated with dialysis for more than 3.7 years prior to randomization had a lower risk of death with high- vs. low-flux dialyzers, whereas there was no difference among those with fewer years of prior HD.
2	Locatelli (2009), [MPO Study]	RCT	647	318	329	No significant difference in mortality with high- vs. low-flux membranes. A statistically significant reduction in all-cause mortality in the high-flux vs. the low-flux group among participants with serum albumin equal to or lower than 4 g/dL (RR 0.49, 95% CI 0.28-0.87). Improved survival associated with high- vs. low-flux dialyzers among those with diabetes.

3	Asci (2013), [EGE Study]	RCT	704	352	352	No statistically significant difference in the composite CV outcome between high- and low-flux dialyzers (HR 0.73, 95% CI 0.49-1.08, *P* = 0.1). Post hoc analysis suggested a benefit associated with high- vs. low-flux dialysis on improving CV event–free survival among those with AV fistulas and those with diabetes.
4	Ayli (2005)	RCT	48	24	24	In the high-flux group, the reduction of β2-MG and P levels during dialysis was significantly higher when compared with the low-flux group (*P* <0.001). During the follow-up period, while β2-MG levels decreased significantly in the high-flux group (*P* <0.05), there was an increase in the low-flux group (*P* <0.05).
5	Chazot (2015)	RCT, cross-over	70	32	38	Average β2-MG was significantly lower at the end of the high-flux phase (43.3 ± 11.1 mg/l vs 27.5 ± 76.0 mg/l, *P* <0.0001) vs. end of low-flux phase.
6	Küchle (1996)	RCT	24	12	12	After 6 years of follow-up no clinical signs of dialysis-related amyloidosis were found in any of the patients dialyzed with high-flux polysulfone membranes, whereas 8/10 of the conventionally dialyzed patients had carpal tunnel syndrome and/or osteoarticular lesions. Serum levels of β2-MG were significantly reduced in patients treated with high-flux polysulfone membranes.
7	Lang (2001)	RCT	30	15	15	Residual renal function declined faster in patients with bioincompatible (cuprophane, low flux) than with biocompatible (polysulfone, high flux) HD membranes (3.6 mL/min vs. 1.9 mL/min after 6 months). Eleven percent of the HD sessions were complicated by clinically relevant blood pressure reductions, but there were no differences between the two dialyzer membrane groups.
8	Li (2010)	randomized, crossover study	45	21	24	Predialysis β2-MG levels decreased significantly when using the high-flux polyamide membrane. No difference between membranes was observed for serum albumin, high-sensitivity C-reactive protein, fibrinogen, IL-6, triglycerides, HDL cholesterol, LDL cholesterol, and lipoprotein(a) during the study. A significant increase in aortic PWV, a marker of aortic stiffness, was noted after patients switched from high-flux to low-flux polyamide membranes.

9	Locatelli (1996)	RCT	155	51	104	Compared Cuprophan hemodialysis (Cu-HD), low-flux polysulfone hemodialysis (LfPS-HD), high-flux polysulfone high-flux hemodialysis (HfPS-HD), and high-flux polysulfone hemodiafiltration (HfPS-HDF). A significant decrease in pre-dialysis plasma β2-MG levels in high-flux dialysis of 9.04 ± 10.46 mg/l (23%) and in hemodiafiltration of 6.35 ± 12.28 mg/l (16%), both using high-flux polysulfone membrane in comparison with cuprophan and low-flux polysulfone membranes (P = 0.032).
10	Locatelli (2000)]	RCT	74	35	39	No difference in hemoglobin level increase between patients treated for 3 months with a high-flux biocompatible membrane in comparison with those treated with a standard membrane.
11	Simon (1993)	RCT	54	32	22	32 were treated with AN 69 (M/F = 13/19, 62 ± 14 years) and 22 with cuprophane. Better survival (70%) at four years was observed in patients with high TACurea who were treated by AN 69. The difference was highly significant with the survival rate (22%) in patients with high TACurea who were treated by cuprophane.
12	Klemm (2004)	RCT, cross-over	26	13	13	No differences between polysulfone high- and low-flux membranes for lowering predialytic serum concentrations of the measured AGEs, which are mainly bound on albumin.

AGE: advanced glycation end-products; AN: acrylonitrile; β2-MG: β2-microglobulin; CV, cardiovascular; HDL: high density lipoprotein; LDL: low density lipoprotein; PWV: pulse wave velocity; TACurea: time-averaged concentration of urea

Key question 3.2.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results

1	Ercan Ok (2013)	RCT	782	391	391	The filtration volume in OL-HDF was 17.2 ± 1.3 L. Primary outcome was not different between the groups (event-free survival of 77.6% in OL-HDF vs. 74.8% in the high-flux group, *P* = 0.28), as well as cardiovascular and overall survival, hospitalization rate and number of hypotensive episodes. In a post hoc analysis, the subgroup of OL-HDF patients treated with a median substitution volume >17.4 L per session (high-efficiency OL-HDF, n = 195) had better cardiovascular (*P* = 0.002) and overall survival (*P* = 0.03) compared with the high-flux HD group. In adjusted Cox-regression analysis, treatment with high-efficiency OL-HDF was associated with a 46% risk reduction for overall mortality (RR 0.54, 95% CI 0.31–0.93, *P* = 0.02) and a 71% risk reduction for cardiovascular mortality (RR 0.29, 95% CI 0.12–0.65, *P* = 0.003) compared with high-flux HD.
2	Marion Morena (2017)	RCT	381	190	191	During the observational period for intradialytic tolerance, 85% and 84% of patients in high-flux hemodialysis and online hemodiafiltration arms, respectively, experienced at least one adverse event without significant difference between groups. As exploratory analysis, intradialytic tolerance was also studied, considering the sessions as a statistical unit according to treatment actually received. Over a total of 11,981 sessions, 2,935 were complicated by the occurrence of at least one adverse event, with a significantly lower occurrence in OL-HDF with fewer episodes of intradialytic symptomatic hypotension and muscle cramps. By contrast, health related QoL, morbidity, and mortality were not different in both groups. An improvement in the control of metabolic bone disease biomarkers and b2-microglobulin level without change in serum albumin concentration was observed with OL-HDF.
3	Francisco Maduell (2013)	RCT	906	456	450	Compared with patients who continued on hemodialysis, those assigned to OL-HDF had a 30% lower risk of all-cause mortality (HR 0.70, 95% CI 0.53–0.92, *P* = 0.01), a 33% lower risk of cardiovascular mortality (HR 0.67, 95% CI 0.44–1.02, *P* = 0.06), and a 55% lower risk of infection-related mortality (HR 0.45, 95% CI, 0.21–0.96, *P* = 0.03). The estimated number needed to treat suggested that switching eight patients from HD to OL-HDF may prevent one annual death. The incidence rates of dialysis sessions complicated by hypotension and of all-cause hospitalization were lower in patients assigned to OL-HDF.

4	Tatsuya Suwabe (2018)	SR	1,412	706	706	Six moderate quality RCTs met the inclusion criteria. Meta-analysis of 4 RCTs including a total of 1,209 patients showed that OL-HDF was associated with a lower yet non-significant score of PCS: MD -0.77 (95% CI -1.94 to 0.41, *P* = 0.20), and MCS: MD -1.25 (95% CI -3.10 to 0.59, *P* = 0.18); indicating a poorer QoL in patients on OL-HDF. Meta-analysis of 4 RCTs including a total of 845 patients showed OL-HDF was associated with a significant increase in the score of social activity compared to HD: SMD (standardized mean difference): 1.95 (95% CI 0.05-3.86, *P* = 0.04), indicating a better QoL in patients on OLHDF; but regarding fatigue and emotion, there was no significant improvement when compared to HD by meta-analysis of 3 RCTs (133 patients).

CI, confidence interval; HD, hemodialysis; HR, hazard ratio; MCS, mental component score; MD, mean difference; OL-HDF, online hemodiafiltration; PCS, physical component score; RCT, randomized controlled trial; RR, relative risk; SR, systematic review; QoL, quality of life

Key question 4.1.

No.	Author (Year)	Study type	Total N	Intervention (n)	Comparison (n)	Study results
1	Bambauer (1990)	Single-center, cross-over, randomized study, 6 months	27 (12 male, 15 female)	LMWH (dalteparin) (27)	UFH (27)	3 bleeding complications with LMWH and 6 with UFH. Sh thrombosis occurred in one patient in UFH group and 3 patients in LMWH.
2	Lord (2002)	Single-center, cross-over, randomized study, 4 wks	32 (17 male, 15 female)	LMWH (tinzaparin) (32)	UFH (32)	Among the 30 patients who completed the study, 2 reported excessive bleeding from their vascular access with tinzapari whereas 8 reported such an excessive bleeding with standar heparin. The presence of clot(s) was observed in the arteria and venous bubble traps in, respectively, 18 ± 12 and 10 ± 6 of the sessions with tinzaparin, while in, respectively, 3 ± 4 and 2 ± 4% of the sessions with standard heparin (*P* <0.005 (32 circuit thrombosis of 378 sessions with LMWH, 21 of 3 with UFH).

3	Nurmohamed (1991)	Single-center, RCT, 6 months	70	LMWH (nadroparin) (35)	UFH (35)	No major bleeding or adverse events were encountered duri a total of 4,000 dialysis procedures (2,000 with LMWH). 3 withdrawals due to puncture site bleeding in LMWH group Clot formation in the extracorporeal circuit was minimal an comparable between the groups at 4, 13, and 26 wks after th start of the study.
4	Saltissi (1999)	Single-center, cross-over, randomized study, 12 wks	36 (17 male, 19 female)	LMWH (enoxaparin) (36)	UFH (36)	12 (1 severe, 11 moderate) bleedings in LMWH vs. 6 (6 moderate) in UFH group; 17 circuit thrombosis (grades ≥5 of 10 defines significant clotting) of 1,111 HD sessions in LMWH vs. 35 of 1,141 in UFH group.
5	Schrader (1988)	Multi-center, RCT, 12 months	70 (40 male, 30 female), incident patients	LMWH (dalteparin) (35)	UFH (35)	No bleeding complications were seen with either heparin. similar incidences of thrombus formation in the extracorpor circulation: 1.59% (80 of 5,045) and 1.33% (69 of 5,197 procedures) for LMW and UF heparin, respectively.
6	Stefoni (2002)	Single-center, cross-over, randomized study, 18 months	54 (39 male, 25 female)	LMWH (nadroparin) (54)	Standard heparin (SH) (54)	During both LMWH and SH sessions no clotting or major bleeding complications were observed. With SH, 7 minor bleeding episodes were observed (zero with LMWH).
Excluded studies from meta-analysis						
1	Borm (1996)	Single-center, cross-over, randomized study (assessed in a single session)	10	LMWH (dalteparin) (10	UFH (10)	No bleeding complications were observed in any patient. Investigation of the extracorporeal circuits revealed a few small clots in 4 of each 10 dialysis procedures.
2	Koutsikos (1996)	Single-center, cross-over, non-randomized study, 1 wk	8 (5 male, 3 female)	LMWH (tinzaparin) (8)	UFH (8)	The mean compression time was longer with UFH than LMWH (14.7 ± 5.8 to 10.3 ± 4.7 min, P <0.05). Circuit thrombosis was observed in 9 out of 24 in LMWH vs. 2 of in UFH groups.

3	Ryan (1991)	Single-center, cross-over, randomized study, 1 wk (dose finding study)	8	LMWH (tinzaparin) (8)	UFH (8)	Excessive clot formation in the dialyzer bubble trap, necessitating additional UFH to enable completion of a prolonged (up to 7 h) dialysis, was observed in all patients c the 1,250 AFXa u dose (mean duration of dialysis prior to UFH, 3 h) but in a single patient only receiving the other LMWH doses.
4	Al-Saran (2010)	Single-center, cross-over, non-randomized study, 6 months	23 (17 male, 6 female)	LMWH (tinzaparin) (23)	UFH (23)	Anticoagulation with tinzaparin sodium resulted in less frequent dialyzer and air-trap clotting compared to UFH (*P* 0.01 and 0.04 respectively). Minor hemorrhages in 3 patien with tinzaparin.
5	Bramham (2008)	Single-center, cross-over, non-randomized study, 2 months	108 (65 male, 43 female)	LMWH (tinzaparin) (108)	UFH (108)	The total number of clotted circuits tended to decrease after the switch to LMWH (34 of 1,489 vs. 13 of 1,823) but was not statistically significant. There were four minor non-access-related episodes of hemorrhage while on treatment with UFH and none with tinzaparin.
6	Yang (1998), short-term test	Single-center, cross-over, non-randomized study, 2 wks	10 (7 male, 3 female)	LMWH (nadroparin) (10)	UFH (10)	No abnormal bleeding episode was observed in the trial period. Eight episodes in 60 dialysis sessions were observed in LMWH to have pinkish remains which was less than 1/3 the dialyzer, whereas 11 episodes were observed in 60 dialy sessions with UF heparin.
7	Sabry (2009)	Single-center, cross-over, non-randomized study, 6 months	23 (17 male, 6 female)	LMWH (tinzaparin) (23)	UFH (23)	3 minor bleeding with LMWH vs. no episodes with UFH; a trap clotting in 9 vs. 13 and dialyzer clotting in 2 vs. 8 patie with LMWH and UFH, respectively.

h, hours; LMWH, low-molecular-weight heparin; min, minutes; RCT, randomized controlled trial; SH, standard heparin; UFH, unfrationated heparin; wks, weeks

Key question 4.2.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Kim (2004)	Crossover trial	58	Nafamostat (58)	Low dose heparin (22)	The exacerbation of bleeding by hemodialysis was noted in only 4% in heparin treated group and none in nafamostat group. Degrees of residual blood in the dialyzer and blood clottings in the venous drip-chamber were less in nafamostat than in heparin group. Nafamostat is a safe and effective regional anticoagulant

						for HD especially for patients with high bleeding risk.
2	Yang (2009)	RCT	17	Nafamostat (8)	Heparin (9)	Nafamostat mesylate has a similar profile of anti-coagulative activity to heparin. It is assumed, however, that nafamostat has an affirmative effect on the recovery of damaged sites following the onset of cerebral hemorrhage. It is an anti-coagulant that can be safely used for HD following the onset of cerebral hemorrhage.

HD, hemodialysis; RCT, randomized controlled trial

Key question 5.1.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Leggat (1998)	Cohort (retrospective),	6,251	IDWG ≤5.7%	IDWG >5.7%	BW gain ≥5.7% leads to a poor prognosis (IDWG >5.7%, adjust HR 1.35, 95% CI 1.16-1.58).
2	Foley (2002)	Cohort (retrospective),	11,242	IDWG ≤2.3%	IDWG >4.8%	BW gain ≥4.8% leads to a poor prognosis (>4.8% group vs. ≤2.3% [ref]; adjusted HR 1.12, 95% CI 1.02-1.23; highest group showed significance only).
3	Saran (2003)	Cohort (prospective)	14,930	IDWG ≤5.7%	IDWG >5.7%	IDWG > 5.7% of DW, adjusted HR 1.12 (95% CI 1.00–1.26), (OR by non-adherence defined by Skipped ≥1 HD session/month aHR 1.30, shortened session by ≥10 minutes aHR 1.11).
4	Stegmayr (2006)	Cohort (prospective)	88	IDWG ≤5.7%	IDWG 2.5-5.7	Mortality rate is the lowest in patients with a BW gain in the range of 2.5–5.7% of DW
5	Kalantar (2009)	Cohort (retrospective),	34,107	Q1,2, ref, Q4,5,6,7,8	Q3, 1.5–2.0kg (n=4,630)	Multivariate adjustment for demographics (case mix) and surrogates of malnutrition-inflammation complex, higher weight-gain increments were associated with increased risk of all-cause and cardiovascular death. HRs of CV death for WG <1.0 kg and ≥4.0 kg (1.5 to 2.0 kg as the ref) were 0.67 (95% CI 0.58 to 0.76) and 1.25 (95% CI 1.12 to 1.39), respectively.
6	Lee (2014)	Cohort (prospective)	1,013	IDWG% Q1 <1.0, Q3, 2.0–2.9, Q4 3.0–3.9, and Q5 ≥4.0 groups	Q2, 1.0–1.9	Q4 1.80 (95% CI 0.95–3.41, *P* = 0.07), Q5 1.93 (95% CI 1.02–3.64, *P* = 0.04), residual renal function and 24-hour urine volume were adjusted, IDWG% ≥4.0 remained as a significant predictor of primary outcome (HR 2.03, 95% CI 1.02–4.02, *P* = 0.04).

7	Stefansson (2014)	Cohort (retrospective),	39,497	IDWG <3%.	IDWG >3.0%	Relative IDWG is defined as IDWG as a percentage of postdialysis weight, Intradialytic hypotension was incrementally greater with greater IDWG. According to this analysis, IDH was least prevalent in patients who experienced relative IDWG <3%.
8	Kurita (2017)	Cohort (prospective)	8,661	Q1,2, ref, Q4,5,6,7	Q3 (n=1,929) 3 to <4%	Albumin ≥ 3.8g/dl Q1, 1.12 (0.64-1.93), Q2, 0.92 (0.49-1.75) 1 (reference), Q7, 2.74* (1.49-5.05) Albumin < 3.8g/dl Q1,1.89* (1.50-2.39), Q2, 1.30 (0.99-1.71) 1 (reference) Q4*, 0.75 (0.58-0.96), Q7, 0.98 (0.62-1.57), for all-cause mortality.
9	Toida (2017)	Cohort (prospective)	1,375	IDWG <5.4%, stratified by Hb level.	IDWG ≥5.4%, stratified by Hb level.	Significant only in Hemoglobin <9 g/dl, compared to ref (9-9.9g/dl) in IDWG <5.4% patients, the correlation between lower Hb levels and all-cause mortality disappeared in high IDWG patients, but was maintained in low IDWG patients (adjusted HRs 3.058, 95% CI 1.575–5.934).
10	Wong (2017)	Cohort (prospective)	21,919	Q4 2.5%-3.99%, N= 8,677	Q1 <0%, Q2 0%-0.99%, Q3 1%-2.49%, Q5, 4%-5.69%, and Q6 ≥5.7%	Compared to relative IDWG of 2.5% to 3.99%, there was elevated risk for mortality with relative IDWG ≥5.7% (adjusted HR 1.23, 95% CI 1.08-1.40), IDWG declined in the United States (20.29 kg; 20.5% of post-HD weight), Canada (20.25 kg; 20.8%), and Europe (20.22 kg; 20.5%), with more modest declines in Japan and Australia/New Zealand
11	Hecking (2018)	Cohort (retrospective),	3,814	IDWG Q2 (2.4–3.6%), (N=9,654)	IDWG Q1 (<2.4%) (N=9,653) IDWG Q3(3.6-5.2) (N=9,653) IDWG Q4(>5.2) (N=9,654)	IDWG Q1 (<2.4%) (HR 1.30, 95% CI 1.20-1.42), IDWG Q3 (3.6-5.2) (HR 0.99, 95% CI 0.90-1.10), IDWG Q4(>5.2) (HR 0.98, 95% CI 0.89-4.08), Total effect adj. for Fl Over post HD using BCM, Greater fluid overload and lower interdialytic weight gain are independently associated with mortality.
12	Dantas (2019)	Cohort (prospective)	255	IDWG <3% of DW (N=75), ref	IDWG 3–3.99% of DW (N=83) IDWG ≥4% of DW (N=97)	IDWG ≥4%, HR of 2.02 (95% CI 1.17–3.49, *P* = 0.012), IDWG 3–3.99%, HR of 0.89 (95% CI 0.49–1.61, *P* = 0.69) for all-cause mortality, (No significance for CV mortality.

aHR, adjusted hazard ratio; BW, body weight; CI, confidence interval; CV, cardiovascular; DW, dry weight; Hb, hemoglobin; HD, hemodialysis; HR, hazard ratio; IDWG, interdialytic weight gain; Q, group divided into categories

Key question 5.2.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Liu (2016)	RCT	64	Intervention group (n = 32), dialysate sodium was switched to 136 mEq/L	Control group (n = 32), dialysate sodium concentration at 138 mEq/L	Values for interdialytic weight gain and pre-HD plasma sodium decreased in the intervention group only. Increasing dialysis sodium removal was associated with improvements in arterial stiffness, left ventricular hypertrophy, and better BP control in hypertensive HD patients.
2	Beduschi (2013)	RCT	52	Dialysate [Na^+]: 135 mEq/L	Dialysate [Na^+]: 138 mEq/L	Inflammatory, biochemical, hematological, and nutritional markers were assessed at baseline and after 8 and 16 weeks. Baseline characteristics were not significantly different between the two groups. Group A showed a significant reduction in serum concentrations of tumor necrosis factor-α, and interleukin-6 over the study period, while the BP and ECW did not change. In Group B, there were no changes in serum concentrations of inflammatory markers, BP, and ECW. Dialysate sodium reduction is associated with attenuation of the inflammatory state, without changes in the BP and ECW, suggesting inhibition of a salt-induced inflammatory response.
3	Boquin (1977)	RCT	51	Dialysate [Na^+]: 130 mEq/L	Dialysate [Na^+]: 140 mEq/L	The interdialytic weight gain was greater with Na 140 than with Na 130, but this greater fluid accumulation was satisfactorily removed during dialysis.
4	Kooman (2000)	Controlled before-and-after study	18	Dialysate sodium concentration to 135 mEq/L	Dialysate sodium concentration from 140 mEq/L	There was considerable pressure in hypertensive dialysis patients, whereas the blood variation using the normal sampling method and markedly pressure drop during dialysis tended to be higher when less using the protocol (Coefficient of Variation range dialysate sodium was reduced).
5	Sayarliogl u (2007)	Controlled before-and-after study	7	Dialysate sodium concentration 135-137 mEq/L	Dialysate sodium concentration 140 mEq/L	In terms of echocardiographic parameters, LVSD, TR, PAP, and IVCD were statistically decreased after low sodium dialysate treatments (P = 0.002, 0.04, 0.013, and 0.00, respectively). Predialysis systolic and diastolic BP, postdialysis systolic BP, and IDWG were statistically decreased when compared to basal levels.

6	Zhou (2013)	Controlled before-and-after study	16	Dialysate sodium concentration 136 mEq/L	Dialysate sodium concentration 138 mEq/L	Along with lowering dialysate sodium, there were significant decreases (–10 mmHg and –6 mmHg) in 44-hour ambulatory systolic and diastolic BP at 4 months. IDWG adjusted to the estimated dry weight mildly but significantly decreased (4.81 ± 1.51 vs. 4.36 ± 1.37%, $P = 0.047$).
7	Arramreddy (2012)	Controlled before-and-after study	13	Dialysate sodium concentration 130-139 mEq/L	Dialysate sodium concentration 140 mEq/L	At the beginning of the observation period, the pre-hemodialysis (HD) plasma Na^+ concentration ranged from 130 to 141 mEq/L. When switched from the standard to the individualized dialysate Na+ concentration, IDWG % decreased from 3.4%, 1.6% to 2.5%, 1.0% ($P = 0.003$) with no change in pre- or post-HD systolic or diastolic blood pressures (all $P > 0.05$).
8	Akyol (2017)	Controlled before-and-after study	HD patients (49)	Dialysate sodium concentration 137 mEq/L	Dialysate sodium concentration 140 mEq/L	Six months after low Na hemodialysis, a decrease was observed in echocardiographic parameters such as PAP and IVCD ($P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively).

BP, blood pressure; ECW, extracellular water; HD, hemodialysis; IDWG, Interdialytic weight gain; IVCD, inferior vein cava diameter; LVSD, left ventricular systolic diameter; PAP, pulmonary artery pressure; TR, tricuspid regurgitation

Key question 6.1.

Not applicable

Key question 6.2.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Selby (2006)	Randomized crossover trial	10	35°C (10)	37°C (10)	Reducing the temperature of the dialysate is an effective intervention to lessen the development of RWMA and also is associated with improved hemodynamics and less intradialytic hypotension.
2	Chesterton (2009)	Randomized crossover trial	10	35°C (10)	37°C (10)	Cool temperature dialysis can be successfully delivered in chronic HD patients and has been shown to be associated with increased baroreflex sensitivity variability, greater peripheral pressor responses and consequently, improved hemodynamic stability.

3	Fine (1996)	Randomized crossover trial	128	35°C (128)	37°C (128)	The incidence of symptomatic hypotension in all patients dialyzed against 35°C was 5.5% compared with 11.2% in all patients dialyzed against 37°C.
4	Jost (1993)	Randomized crossover trial	12	35°C (12)	37°C (12)	Thus, 35°C dialysate significantly improves the hemodynamic tolerance to hemodialysis in hypotension-prone and large weight gainer patient groups and also reduces the incidence of symptomatic hypotension.
5	Jefferies (2011)	Randomized crossover trial	11	Individualized temperature	37°C (11)	Intradialytic systolic BP was higher during individualized HD vs. HD 37°C. Individualized-temperature HD abrogates stunning, providing effective hemodynamic stabilization at no additional therapy cost.
6	Ayoub (2004)	Randomized crossover trial	10	35°C (10)	36.5°C (10)	Cool dialysate improves tolerance for dialysis in hypotensive patients and helps increase ultrafiltration while maintaining hemodynamic stability during and after dialysis.
7	Maggiore (2002)	Randomized crossover trial	95	Isothermic (95)	Thermoneutral (95)	Results show that active control of body temperature can significantly improve intradialytic tolerance in hypotension-prone patients.
8	Cruz (1999)	Prospective crossover study	11	35.5°C (11) or 35.5°C with midodrine (11)	37°C (11)	Cool dialysate are effective therapies for intradialytic hypotension. Cool dialysate improved intradialytic and post-HD blood pressures and reduced the frequency of hypotensive episodes and the number of interventions required for intradialytic hypotension.
9	Hegbrant (1994)	Prospective crossover study	10	34.5°C (10)	36.5°C (10), 38.5°C (10)	A significant decrease in mean arterial blood pressure during warm HD, while during cold HD it remained stable.
10	Azar (2009)	Prospective crossover study	50	35°C (50)	37°C (50)	Low temperature dialysate is particularly beneficial for highly symptomatic patients, improves tolerance to dialysis in hypotensive patients and helps increase ultrafiltration while maintaining hemodynamic stability during and after dialysis.

BP, blood pressure; HD, hemodialysis; RWMA, regional wall motion abnormality

Key question 7.1.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Eknoyan (2002)	RCT	1,846	High-dose (920)	Standard dose (920)	Patients are evaluated on Routine kinetic modeling Monthly.
2	Thomas (2020)	Retrospective Cohort study	7,454	Every 6 weeks blood sampling (n=2,119)	Monthly blood sampling (n=5,335)	Monthly routine blood testing in HD recipients was not associated with a lower risk for death, cardiovascular events, or hospitalizations as compared with testing every 6 weeks.

HD, hemodialysis; RCT, randomized controlled trial

Key question 8.1.

No.	Author (year)	Study type	Total (n)	Intervention [n / (death)]	Comparison [n / (death)]	Study results
1	Smith (2003)	Cohort (retrospective)	321	258 / (41)	63 / (34)	Older patients with multiple co-morbidities and poor performance status, may not extend life, In high-risk, highly dependent patients with renal failure, the decision to dialyze or not has little impact on survival. No difference.
2	Joly (2003)	Cohort (retrospective)	144	101 / (60)	43 / (37)	Octogenarians who were dialyzed, survived longer than those not offered dialysis, though the latter were more dependent, more socially excluded, more had been referred late, and more were diabetic.
3	Murtagh (2007)	Cohort (retrospective)	129	52 / (12)	77 / (51)	Older patients with multiple co-morbidities and poor performance status, may not extend life. No difference.
4	Carson (2009)	Cohort (prospective)	202	173 / (100)	29 / (25)	Dialysis prolongs survival for elderly patients who have ESRD with significant comorbidity by approximately 2 years.
5	Brown, (2015)	Cohort (prospective)	395	273 / (28)	122 / (68)	Compared with the RSC-NFD group, the death rate was lower in the predialysis group who did not require dialysis (HR 0.23, 95% CI 0.12-0.41) and in those requiring dialysis (HR 0.30, 95% CI 0.13-0.67, P = 0.004) but not in dialysis patients who had not attended the

						predialysis clinic (HR 0.60, 95% CI 0.35-1.03). No significant survival advantage of choosing RRT in patients ages >75 years old with two or more comorbidities, although the number of these patients was small.
6	Verberne (2016)	Cohort (retrospective)	311	204 / (111)	107 / (69)	From those who started with RRT (n = 122), 79% (n = 96) started on HD, and 21% started on PD (n = 26). Four patients underwent renal transplantation, three of them after having started dialysis. Choice of RRT was associated with lower mortality (HR 0.62, 95% CI 0.42-0.92, *P* = 0.02)
7	Reindl-Schwaighofer (2017)	Cohort (retrospective)	8,796	8,622 / (7,755)	174 / (173)	Hemodialysis treatment was associated with a decreased risk for death with a HR of 0.23 (95% CI 0.18-0.29; *P* <0.001) compared to conservative treatment.
8	Raman (2018)	Cohort (prospective)	204	123 / (72)	81 / (67)	The adjusted HR for death in the dialysis group compared to CC was 0.61 (0.41–0.61, *P* = 0.01).
9	Tam-Tham (2018)	Cohort (retrospective)	838	500 / (305)	338 / (285)	Using a marginal structural Cox model, treatment with dialysis was associated with a lower risk of all-cause mortality in the first 3 years of follow-up (HR 0.59, 95% CI 0.46–0.77, *P* < 0.001).
10	van Loon (2019)	Cohort (prospective)	281	192 / (31)	89 / (31)	After adjusting for age, comorbidity level and GFR category, HR for twelve-month mortality for conservative care vs. dialysis was 2.12 (95% CI 1.12–4.03). QoL: a small decline of QoL was found for conservative patients, while QoL did not change in dialysis patients.
11	Pyart (2020)	Cohort (retrospective)	1,216	841 / (420)	375 / (262)	On adding choice to the model, higher comorbidity and older age remained associated with higher mortality but choosing RRT over MCM also predicted survival. Frailty and age were better predictors of survival than comorbidity and in patients with at least moderate frailty, RRT offered no survival benefit over MCM.
12	Tam-Tham 2020	Cohort (retrospective)	968	557 / (221)	411 / (163)	Hospitalization: patients who underwent dialysis spent more adjusted in-hospital days per person-year (36.25, 95% CI 30.72-41.77 vs. 14.65, 95%CI 12.28-17.02; incidence rate ratio 2.47, 95% CI 1.99-3.08). Among patients who died during follow-up (n = 672), a higher proportion of deaths occurred in a hospital setting among those treated with dialysis than those not treated with dialysis (unadjusted proportions, 221 [66.0%] vs. 163 [48.4%]; adjusted proportions, 66.0% vs. 24.3%; adjusted relative risk 2.93, 95% CI 2.51-3.41).

CC, conservative care; CI, confidence interval; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HD, hemodialysis; HR, hazard ratio; QOL, quality of Life; PD, peritoneal dialysis; RRT, renal replacement therapy; RSC-NFD, renal supportive care without dialysis; MCM, maximum conservative management

Key question 8.2.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Chand (2017)	Position paper				
2	Slerno (2016)	Position paper				
3	Jones (2012)	Book Chapter				
4	BritishjColumbia Nurses' Union (2011)	Position statement				
5	The Royal college of Nursing (2002)	Recommendation				