Supplemental Material

Supplemental Table 1: MeSH terms

Supplemental Figure 1: Summary of evidence search and selection. Performed January 6, 2017.
Note: RCT = randomized controlled trial, CV = cardiovascular, IV = intravenous, CKD = chronic kidney disease.

Supplemental Table 2: Characteristics of randomized controlled trials

Supplemental Figure 2: Bias Assessment Within Randomized Controlled Trials.
Based on Cochrane Collaboration's tool for assessing risk of bias in randomized trials[24].

Supplemental Figure 3: Aggregate Risk of Bias Across Included Randomized Controlled Trials.
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Supplemental Figure 4: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Infection Events in Randomized Controlled Trials at Lower Risk of Bias.

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Supplemental Table 3: Characteristics of observational studies

Supplemental Figure 6: Bias Assessment Observational Studies.
Based on the Newcastle-Ottawa Scale for assessing risk of bias in observational studies[25].

Supplemental Figure 7: Aggregate Risk of Bias Across Included Observational Studies. Based on the Newcastle-Ottawa Scale for assessing risk of bias in observational studies[25].

Supplemental Figure 8: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Mortality Events in Observational Studies at Lower Risk of Bias.

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Supplemental Figure 10: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Cardiovascular Events in Observational Studies at Lower Risk of Bias.

Supplemental Figure 11: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Hospitalization Events in Observational Studies at Lower Risk of Bias.

Supplemental Table 1: MeSH terms

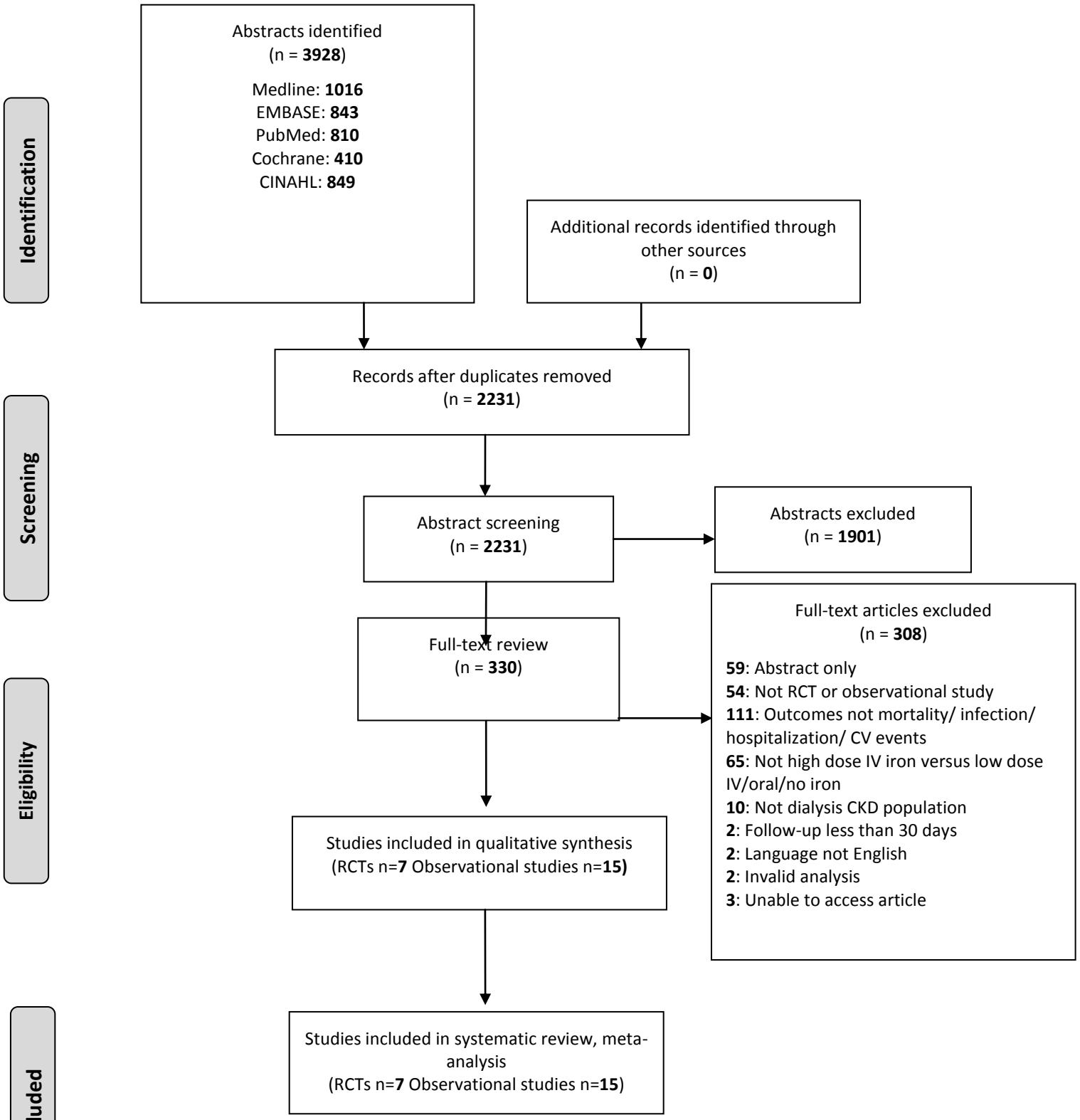
MEDLINE:
1. exp Renal Replacement Therapy/
2. kidney replace$.ti,ab,kw,kf.
3. renal replace$.ti,ab,kw,kf.
4. dialys?s.ti,ab,kw,kf.
5. h?emodialys?s.ti,ab,kw,kf.
6. h?emofiltrat$.ti,ab,kw,kf.
7. h?emodialfiltrat$.ti,ab,kw,kf.
8. or/1-7
9. exp Administration, Intravenous/
10. intravenous.ti,ab,kw,kf.
11. iv.ti,ab,kw,kf.
12. dripinfus$.ti,ab,kw,kf.
13. infusions, parenteral/
14. parenteral.ti,ab,kw,kf.
15. or/9-14
16. Iron/
17. iron.ti,ab,kw,kf.
18. ferrous.ti,ab,kw,kf.
19. ferric.ti,ab,kw,kf.
20. ferretin$.ti,ab,kw,kf.
21. or/16-20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. drugtherapy.fs.
27. randomly.ab.
28. trial.ti,ab.
29. groups.ab.
30. comparative study.sh.
31. comparative stud$.ti,ab,kw,kf.
32. evaluation studies.pt.
33. exp Evaluation Studies as Topic/
34. evaluation stud$.ti,ab,kw,kf.
35. follow up studies.sh.
36. prospective studies.sh.
37. prospective stud$.ti,ab,kw,kf.
38. retrospective studies.sh.
39. retrospective stud$.ti,ab,kw,kf.
40. cohort studies.sh.
41. cohort stud$.ti,ab,kw,kf.
42. (control$ or prospectiv$ or retrospectiv$ or volunteer$ or cohort$).ti,ab.

43. or/22-42
44. exp animals/ not humans.sh.
45. 8 and 15 and 21 and 43
46. 45 not 44
EMBASE:
1. exp renal replacement therapy/
2. kidneyreplac$.ti,ab,kw.
3. renalreplac$.ti,ab,kw.
4. dialys?s.ti,ab,kw.
5. h?emodialys?s.ti,ab,kw.
6. h?emofiltrat$.ti,ab,kw.
7. h?emodiafiltrat$.ti,ab,kw.
8. or/1-7
9. exp intravenous drug administration/
10. intravenous.ti,ab,kw.
11. iv.ti,ab,kw.
12. infusion/
13. dripinfus$.ti,ab,kw.
14. parenteral$.ti,ab,kw.
15. or/9-14
16. iron/
17. iron.ti,ab,kw.
18. ferrous.ti,ab,kw.
19. ferric.ti,ab,kw.
20. ferretin$.ti,ab,kw.
21. or/16-20
22. clinical trial/
23. randomized controlled trial/
24. randomization/
25. single blind procedure/
26. double blind procedure/
27. crossover procedure/
28. placebo/
29. randomi?ed controlled trial$.tw.
30. rct.tw.
31. random allocation.tw.
32. randomly allocated.tw.
33. allocated randomly.tw.
34. (allocated adj2 random).tw.
35. single blind$.tw.
36. double blind$.tw.
37. ((treble or triple) adj blind$).tw.
38. placebo$.tw.
39. comparative study/
40. comparative stud$.ti,ab,kw.

41. exp evaluation studies/
42. evaluation stud$.ti,ab,kw.
43. follow up/
44. prospective study/
45. prospective stud$.ti,ab,kw.
46. retrospective study/
47. retrospective stud$.ti,ab,kw.
48. cohort studies/
49. cohort stud$.ti,ab,kw.
50. (control$ or prospectiv$ or retrospectiv$ or volunteer$ or cohort$).ti,ab.
51. or/22-50
52. case study/
53. case report.tw.
54. abstract report/ or letter/
55. or/52-54
56. exp animals/ not humans/
57. or/55-56
58. 51 not 57
59. 8 and 15 and 21 and 58
PUBMED:
(("renal replacement therapy"[mh] OR "renal replacement therapy"[tw] OR "renal replacement therapies"[tw] OR "kidney replacement therapy"[tw] OR "Kidney replacement therapies"[tw] OR "dialysis"[tw] OR "dialyses"[tw] OR "hemodialysis"[tw] OR "hemodialyses"[tw] OR “haemodialysis"[tw] OR “haemodialyses"[tw] OR “hemofiltrate”[tw] OR “hemofiltration”[tw] OR “haemofiltrate”[tw] OR “haemofiltration”[tw] OR “hemodiafiltrate”[tw] OR “hemodiafiltration”[tw] OR “haemodiafiltrate”[tw] OR “haemodiafiltration”[tw]) AND ("administration, intravenous"[mh] OR "intravenous"[tw] OR “iv”[tw] OR “infusions, parenteral”[MeSH] OR “infusions, intravenous”[mh] OR “infusion"[tw] OR "infusions"[tw]) AND ("iron"[mh] OR iron[tw] OR "ferric"[tw] OR "ferrous"[tw] OR “ferretin”[tw]) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR “placebo”[tiab] OR “drug therapy”[sh] OR "clinical trial"[pt] OR "clinical trials as topic"[mesh] OR randomly[tiab] OR “trial”[ti] OR “groups”[tiab] OR "comparative study"[pt] OR "evaluation studies"[pt] OR “cohort studies”[mh] OR "follow up studies"[mh] OR "prospective studies"[mh] OR “retrospective studies”[mh])) NOT (“animals”[mh] NOT “humans”[mh])
Cochrane:
#1 MeSH descriptor: [Renal Dialysis] explode all trees
#2 MeSH descriptor: [Hemofiltration] explode all trees
#3 renal next replace*
#4 kidney next replace*
#5 Hemodialys*
#6 haemodialys*
#7 hemofiltrat*
#8 haemofiltrat*
#9 hemodiafiltrat*

#10	haemodiafiltrat*
#11	dialys*
#12	{or #1-#11}
#13	MeSH descriptor: [Administration, Intravenous] explode all trees
#14	intravenous
#15	infus*
#16	"IV"
#17	MeSH descriptor: [Infusions, Parenteral] this term only
#18	parenteral
#19	{or #13-#18}
#20	MeSH descriptor: [Iron] this term only
#21	iron
#22	ferrous
#23	Ferric
#24	ferretin*
#25	{or #20-#24}
#26	#12 and #19 and #25
CINAHL:	
S45	S27 AND S44
S44	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR 43
S43	TX allocat* random*
S42	MH"quantitative studies"
S41	MH "placebos"
S40	TX placebo*
S39	TX random* allocat*
S38	MH "random assignment"
S37	(MH "retrospective design") OR (TX cohort*)
S36	(TI "retrospectiv*") OR (AB "retrospectiv*)
S35	(MH "evaluation research")
S34	MH "prospective studies" OR (TI "prospectiv*") OR (AB "prospectiv*")
S33	(MH "comparative studies") OR (TI "comparative stud*") OR (AB "comparative stud*")
S32	TX "randomi* control* trial*"
S31	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S30	TX (clinic* n1 trial*)
S29	PT "clinical trial"
S28	MH "Clinical Trials+"
S27	S8 AND S17 AND S26
S26	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
S25	TX ferrous
S24	TX ferretin*
S23	TX ferric

S22	TX iron
S21	MH "ferric compounds"
S20	MH "ferrous compounds"
S19	MH "Iron Compounds"
S18	(MH "Iron")
S17	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S16	TX "parenteral*"
S15	(MH "Infusions, Parenteral")
S14	(MH "Injections, Intravenous")
S13	TX "infus*"
S12	(MH "Infusions, Intravenous")
S11	TX "IV"
S10	TX "intravenous"
S9	(MH "Administration, Intravenous+")
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S7	(TX "hemodiafiltrat*") OR (TX haemodiafiltrat*)
S6	(TX hemofiltrat*) OR (TX haemofiltrat*)
S5	(TX hemodialys*) OR (TX haemodialys*)
S4	TX dialys*
S3	TX "renal replace*"
S2	TX "kidney replace*"
S1	(MH "Renal Replacement Therapy+")



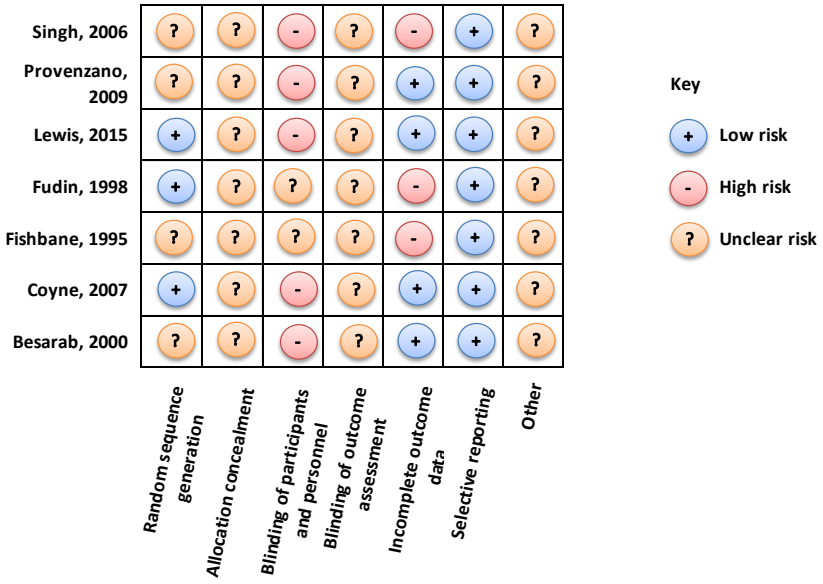
Supplemental Figure 1: Summary of evidence search and selection. Performed January 6, 2017. Note: RCT = randomized controlled trial, CV = cardiovascular, IV = intravenous, CKD = chronic kidney disease.

Supplemental Table 2: Characteristics of randomized controlled trials

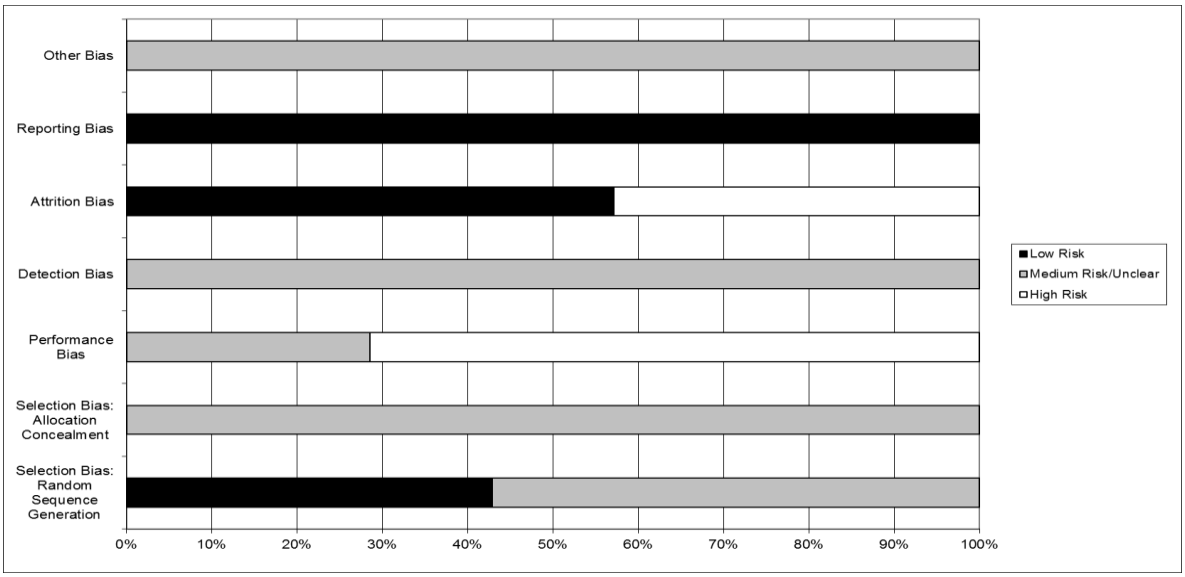
Study: 1st author year of publication year of study study name/data source	**Control/low dose IV iron (0-200mg/month)**	**Active/high dose IV iron (>200mg/month)**	**Control TSAT Baseline F/U**	**Active TSAT Baseline F/U**	**Control/low dose ferritin Baseline F/U**	**Active/high dose ferritin Baseline F/U**	**Control/low dose ESA Baseline F/U**	**Active/high dose ESA Baseline F/U**	**Control/low dose HGB Baseline F/U**	**Active/high dose HGB Baseline F/U**	**Notes**
Fishbane(28) (1995) N/A N/A	N/A	N/A	21.1 (0.8) 19.8 (1.0)	22.7 (3.0) 74.8 (2.9)	178.9 (12.6) 157.3 (15.4)	191.2 (18.1) 753.9 (30.2)	6750 (419) 7563 (378) U/treatment	7100 (571) 4050 (634) U/treatment	31.8 (0.4) 31.8 (0.4) HCT	34.4 (0.7) 32.5 (0.6) HCT	Baseline 4 months
Fudin(29) (1998) N/A N/A	none ferrous sulfate 160mg po daily	250mg	N/A	N/A	none: 190 (96) oral: 204 (115) none: 243.6 (107.5) oral: 229.7 (113.6)	268 (286) 393.5 (249.3)	none	none	none: 63 (10) oral: 68 (8.2) N/A N/A	78 (3) 110 (9)	Baseline 12 months for none, 26 months for oral, IV
Besarab(30) (2000) N/A N/A	795 (119)mg during run-in phase, 141 (46)	568 (120)mg during run-in phase, 504 (21)	23.9 (1.8), 27.6	24.6 (1.7), 32.6	287 (36), 297.5	285 (35), 730.5	3782 (559) U 3x/week, mean 3795 (248) in F/U	3625 (419) U 3x/week Figure 3	10.5 (0.3), 10.3	10.6 (0.1), 10.4	Baseline 6 months
Singh(31) (2006) N/A N/A	None	ID 970.9mg (944.4-997.5)	16.8 Figure 5	19.8 Figure 5	194.2 Figure 5	167.5 Figure 5	7932IU/wk Figure 3	11681IU/wk Figure 3	10.5 Figure 4	10.6 Figure 4	Baseline 70 days
Coyne(32) (2007) 2004-2006 DRIVE N/A	36.9% with 70 (108) mg in baseline in last 4 weeks but overall N/A	34.4% with 61 (103) mg in baseline in last 4 weeks but overall N/A	19.0 (4.1) 21.1 (5.8)	18.2 (4.2) 25.6 (7.6)	765 (193) 591 (274)	759 (190) 929 (297)	35128 (17769) IU/wk + 25%	33498 (17377)IU/wk + 25%	10.2 (0.7) 11.3 (1.4)	10.4 (0.8) 11.9 (1.3)	Baseline, 6 weeks
Provenzano(	3765mg (by pill	FX 992mg	15.91	15.71	358 (172)	341 (159)	N/A	N/A	10.69	10.59 (0.67)	Baseline

33) (2008) N/A N/A	counting estimation)	94.5% 1.02g 5.5% 510mg	(6.29) 16.46 (9.72)	(7.21) 22.31 (13.33)	289.30 (165.76)	601.79 (282.95)	N/A	N/A	(0.57) 11.22 (1.22)	11.72 (1.20)	35 days
Lewis(34) (2015) 2010-2012 N/A	FC by protocol with median 8.0 tablets/ dayand IV iron 12.9 (1.0-28.9) mg/week x 4	26.8 (13.4-47.6) mg/week x 4	29 (24-37) 36.0 (27.5-47.0)	29 (23-35) 28.0 (21.0-34.5)	582 (380-778) 858 (568-1105)	568 (374-780) 576 (333-883)	81.5% on ESA 5303 (2023-9695)	82.6% on ESA 6954 (2664-12375)	11.4 (10.7-12.2) 11.20 (10.50-12.10)	11.7 (10.9-12.4) 11.00 (10.25-12.30)	Baseline 52 weeks

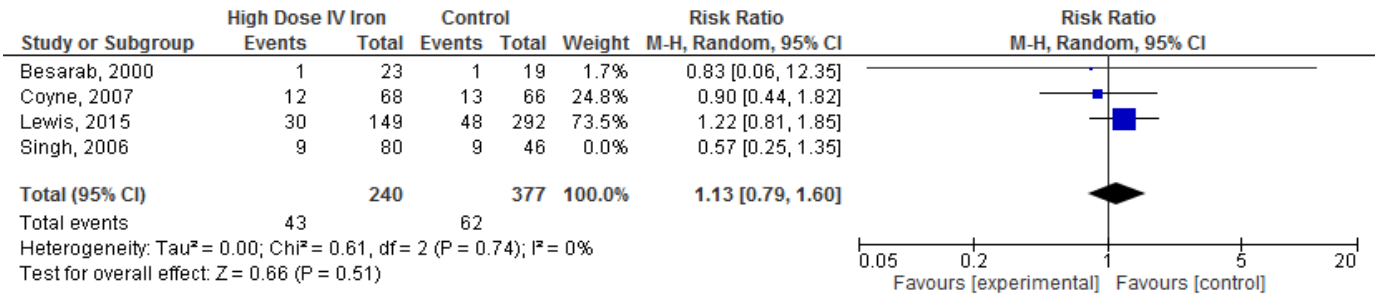
Note: IV = intravenous, TSAT = transferring saturation, ESA = erythropoietin stimulating agent, HGB = hemoglobin, F/U = follow-up, HCT = hematocrit, CFB =, FX = feroxumytol, FC = ferric citrate, N/A = not reported



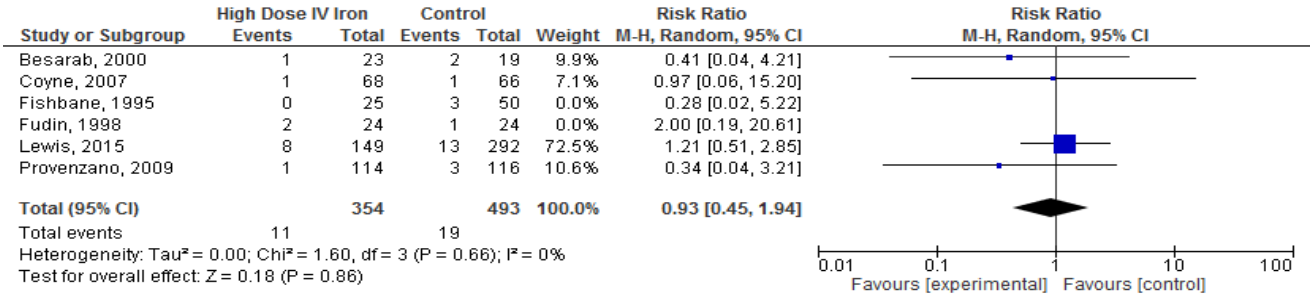
Supplemental Figure 2: Bias Assessment Within Randomized Controlled Trials. Based on Cochrane Collaboration's tool for assessing risk of bias in randomized trials[24].



SupplementalFigure 3: Aggregate Risk of Bias Across Included Randomized Controlled Trials. Based on Cochrane Collaboration's tool for assessing risk of bias in randomized trials[24].



Supplemental Figure 4: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Infection Events in Randomized Controlled Trials at Lower Risk of Bias.



Supplemental Figure 5: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Mortality Events in Randomized Controlled Trials at Lower Risk of Bias.

Supplemental Table 3: Characteristics of observational studies

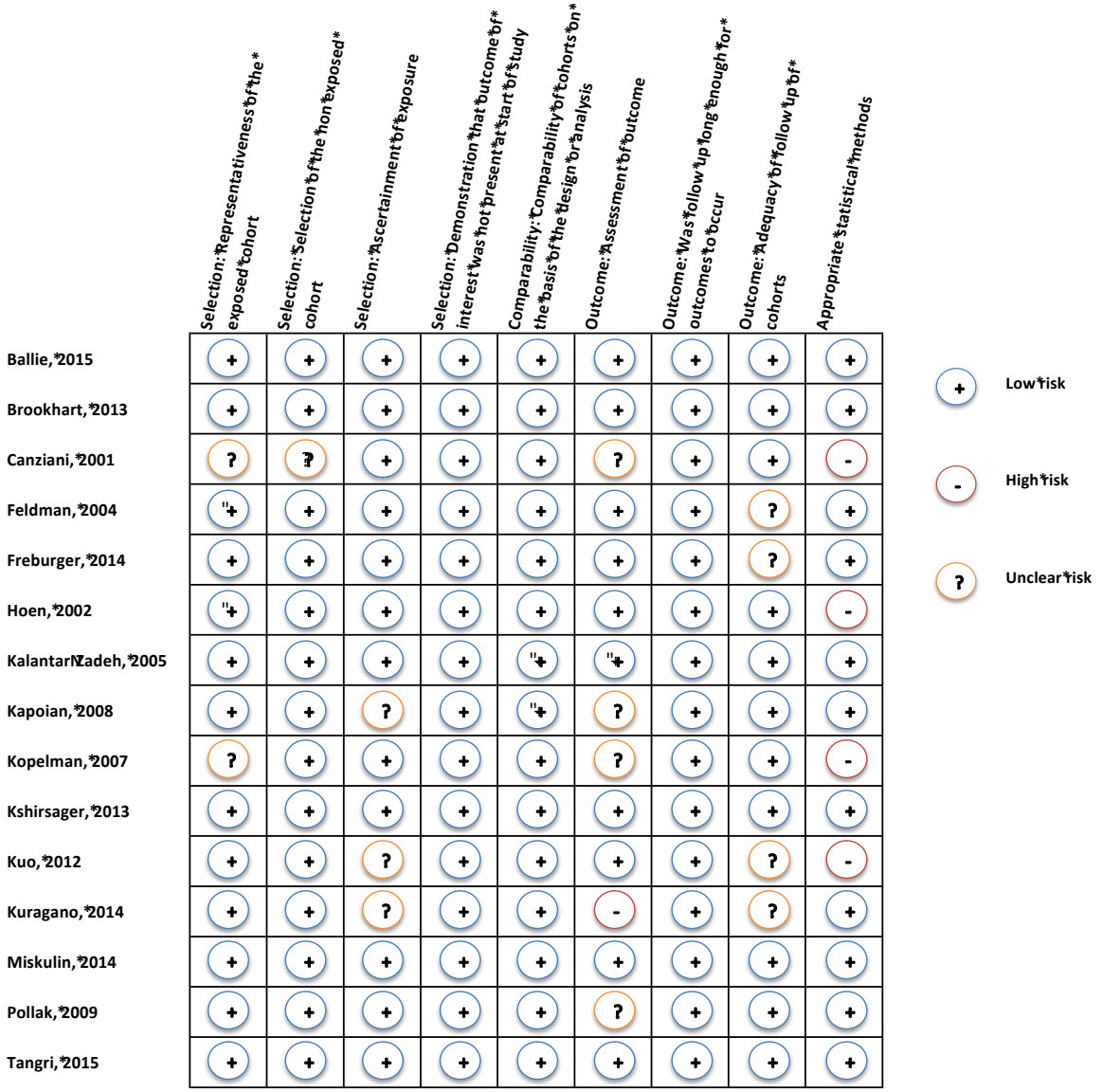
Study: 1st author year of publication year of study study name/data source	**Control/low dose IV iron (0-200mg/month)**	**Active/high dose IV iron (>200mg/month)**	**Control TSAT Baseline F/U**	**Active TSAT Baseline F/U**	**Control/low dose ferritin Baseline F/U**	**Active/high dose ferritin Baseline F/U**	**Control/low dose ESA Baseline F/U**	**Active/high dose ESA Baseline F/U**	**Control/low dose HGB Baseline F/U**	**Active/high dose HGB Baseline F/U**	**Notes**
Canziani(35) (2001) N/A N/A	1g/75 or 150 days = 200-400mg/month 1g/150 days =200mg/month	2g/150 days =400mg/month	13.1 (3.4), 34.9 (86) 61.4 (10.3) 44.0 (40.0)	10.8 (4.7) 38.9 (36.9) %	N/A N/A	N/A N/A	72%, 71% N/A	92% N/A	9.3 (1.8), 10.7 (2.0) 11.1 (2.3), 11.4 (1.9)	8.8 (1.3) 11.3 (2.9)	Baseline 150 days
Hoen (36) (2002) 1994-1995	oral 1258 (358), 1063 (387) mg per week for BE, no BE	IV 187 (86), 151 (89) mg per week for BE, no BE	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	However, in multivariate Cox analysis, neither IV iron administration nor the weekly amount of iron in the subgroup of IV iron-treated patients was retained in the model as significant risk factors for bacteremia
Feldman (37, 38) (2002)(2004) 1996-1998 Fresenius Medical Corporation	27% none 12% 0-700mg 13% >700-1000mg for baseline, 6%, 21%, 17% in F/U over 6 months	23% 1000-1800mg, 25% >1800mg for baseline, 40%, 15% for F/U over 6 months	<20 26.6, 32.0 20-<35 24.8, 25.1 35-<50 30.5, 29.4 ≥50 44.8,	<20 50.5 20-<35 50.1 35-<50 40.1 ≥50 29.0 for	<100 35.4, 23.4 100-<800 22.8, 25.7 ≥800 34.8, 26.4 for none, >0-1000mg baseline	<100 41.2 100-<800 51.6 ≥800 38.8 for >1000mg baseline iron N/A	EPO none 64.5, 13.1 >0-20000 29.5, 30.5 >20000-40000 25.8, 28.5 >40000	EPO none 22.4 >0-20000 40.0 >20000-40000 45.7 >40000 54.1 for >1000mg	<8 32.2, 16.2 8-<10 23.2, 23.3 10-<12 27.6, 26.8 ≥12 40.3, 26.3 for none, >0-1000mg	<8 16.2 8-<10 23.3 10-<12 26.8 ≥12 26.3 for >1000mg baseline	Baseline N/A But only for baseline IV iron status

			26.3 for none, >0-1000mg baseline iron N/A	>1000 mg baseline iron N/A	iron N/A		21.7, 24.2 for none, >0-1000mg baseline iron N/A	baseline iron N/A	baseline iron N/A	iron N/A	
Kalantar-Zadeh(39) (2005) 2001-2003 DaVita	0, 1-199.9mg	200-399.9, ≥400mg	33 (13) N/A	29 (11) N/A	718 (596) N/A	556 (448) N/A	16580 (30440) units/wk N/A	21560 (17660) units/wk N/A	11.8 (1.3) N/A	12.1 (1.3) N/A	Baseline N/A But only for baseline IV iron status
Kopelman(40) (2007) N/A N/A	FG 23 (51)mg over 3 months	FG 1065 (555)mg over 3 months	36.0 (21.0) 32.1 (9.5)	19.9 (2.3) 30.3 (21.3)	1215 (288) 1184 (257)	1040 (160) 1039 (278)	3450 4600IU/HD	6125 4436IU/HD	11.6 (0.8) 11.2 (1.1)	10.0 (0.8) 11.8 (1.9)	Baseline 3 months
Kapoian(41) (2008) N/A DRIVE-2 -control and active groups need to be changed	59% FG or IS median 200mg (0-1250), mean 326 (372)	39% FG or IS median 0mg (0-875), mean 131 (214)	≤800 18.7 (3.6), 19.9 (6.4), 17.6 (6.2) >800 19.6 (4.5), 22.5 (4.6), 21.9 (6.3)	≤800 18.7 (3.6), 25.5 (6.1), 23.7 (12.8) >800 17.5 (4.8), 26.4 (8.6), 25.9 (18.3)	≤800 631 (86), 453 (172), 506 (274) >800 923 (135), 762 (292), 717 (278)	≤800 622 (89), 798 (184), 698 (179) >800 968 (122), 1139 (288), 955 (345)	45.0 (23.5) 37.7 (29.7-54.6) mean change 649 (19987) IU/week, 0 IU/week from 6-12 weeks	43.7 (22.4) 37.5 (26.9-54.8) mean change -7527 (18021) IU/week from 6-12 weeks	≤800 10.2 (0.7), 11.4 (1.1), 11.5 (1.1) >800 10.1 (0.8), 11.4 (1.6), 11.7 (1.8)	≤800 10.3 (0.9), 11.9 (1.4), 12.0 (1.4) >800 10.3 (0.7), 12.0 (1.3), 12.3 (1.3)	Baseline (DRIVE-1) 6 weeks (DRIVE-2) 12 weeks for ferritin ≤800, >800
Pollak(42) (2009) 1998-2006 N/A	0, 1-202	202.1-455,>455	0, 1-202 ≤16 16, 3 16.1-20 14, 6 20.1-25 20, 18 >25 126, 219	202.1-455,>455 ≤16 16, 45 16.1-20 142, 191	0, 1-202 <100 30,23 100.1-300 37. 75 300.1-600 31, 65 600.1-1000 34,	202.1-455,>455 <100 34, 34 100.1-300 162, 124 300.1-600 233, 123	N/A N/A	N/A N/A	N/A N/A	N/A N/A	Baseline N/A median EPO 18.16 (12.10-27.74) 10^3 units/week, IV iron 301.2 (201.6-454.4) mg/month, HGB 116.1g/L, TSAT

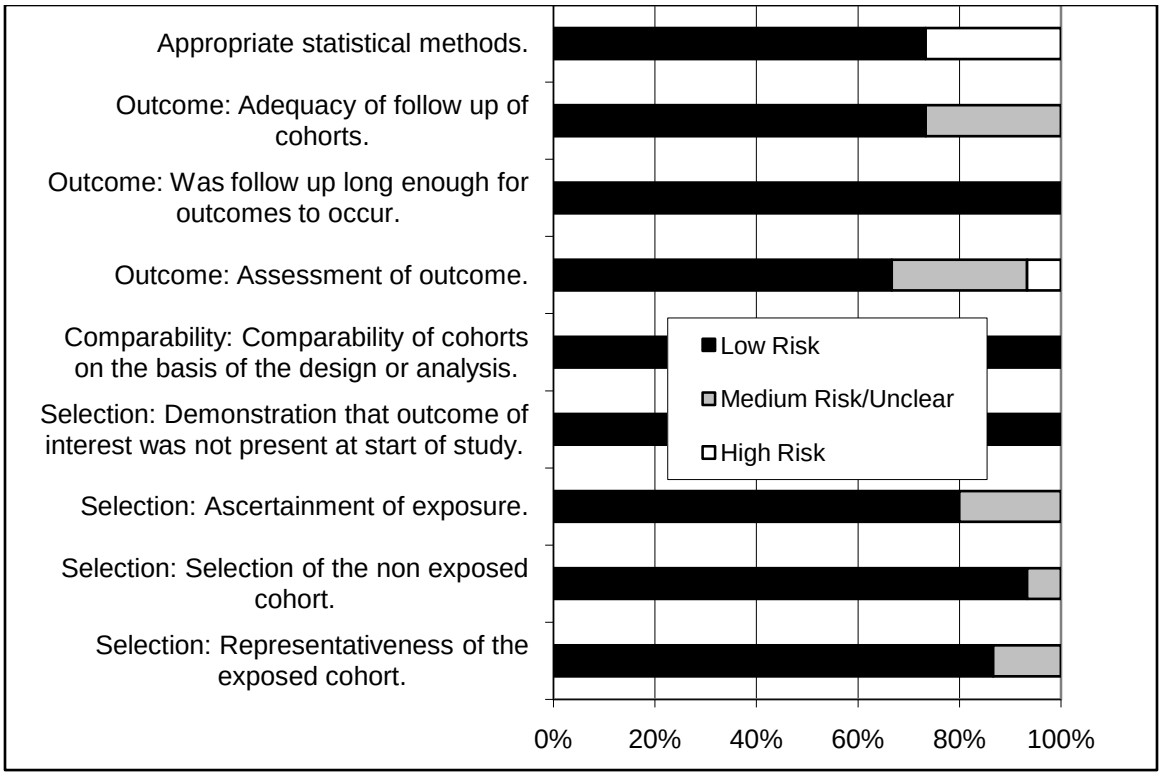
			N/A	20.1-25 >25 695, 263 N/A	52 >1000 29, 28 N/A	600.1- 1000 291, 161 >1000 161, 53 N/A					29.76%, ferritin 562microg/L
Kuo(43) (2012) 2004-2005 N/A	none, 40-800mg over 6 months = 133.3mg/month	840-1600mg 1640-2400mg over 6 months = 140-266.7mg/month, 273.3-400mg/month	N/A N/A	N/A N/A	566 (352,594) 497 (307, 818)	354 (188, 518) 400 (228, 583)	70.3 (41.1) U/kg/week N/A	70.6 (34.9) U/kg/week N/A	10.4 (1.5) 10.2 (1.7)	10.2 (1.7) 10.4 (1.4)	with or without IV iron Baseline 12 months
Brookhart(44) (2013) 2004-2008 USRDS	none, low dose 1-200mg = 125 (100-200)	high dose >200mg 400 (300-700)	31.0 (24.0-41.0), 28.0 (23.0-36.0) N/A	23.0 (18.0-29.0) N/A	743 (473-977), 514 (351-678) N/A	457 (280-641) N/A	47.5 (22.0-94.6), 50.7 (24.2-97.5) 1000u/month N/A	75.0 (36.3-142) 1000u/month N/A	12.2 (11.5-13.0), 12.2 (11.5-13.0) N/A	12.1 (11.3-13.0) N/A	Baseline N/A Also maintenance vs bolus
Kshirsager(45) (2013) 2004-2008 USRDS	none, low dose 200mg/month 135 (34)	high dose 700mg/month 538 (316)	35.0 (15.9), 30.4 (11.4)	24.7 (10.5)	766 (514), 536 (309)	489 (314)	74 (84), 76 (81) units/month	107 (103) units/month	12.2 (1.3), 12.3 (1.2)	12.1 (1.4)	Baseline N/A Also maintenance vs bolus
Freburger(46) (2014) 2006-2010 USRDS	none, maintenance 227 (118)	bolus 700 (291)	35.8 (14.3) 31.4 (10.9)	23.7 (9.5)	862 (588) 745 (536)	625 (479)	63.0 (73.9) 73.1 (77.0)	113 (100)	11.9 (1.4) 12.0 (1.3)	11.5 (1.4)	Baseline N/A
Kuragano(47) (2014) 2007-2009 TRAP	none, low<50mg/week	high ≥50mg/week	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	HGB 10.6 (1.0), ferritin 125.4 (147.0), TSAT 26.7 (11.7(, ESA 3212 (2107) IU/wk
Miskulin(48) (2014) 2003-2008 DEcIDE	no vs low >0-150mg vs moderate >150-350mg vs high	>350mg per month	Ferritin≤500, TSAT≤20 33.1, 37.4, 44.4, 62.9 Ferritin≤500, TSAT 21-30 19.2, 21.8, 25.8, 18.4 Ferritin 501-800, TSAT≤20 4.3, 7.1, 6.5, 5.9 Ferritin>800 21.0, 6.2, 3.0, 2.7				≤5000 9.4, 6.3 5001-12000	≤5000 18.8, 10.4 5001-12000	<10 9.4, 6.3 10.1-11 12.4, 10.0 11.1-12	<10 6.1, 8.6 10.1-11 8.9, 12.3	Baseline N/A

			Ferritin<500, TSAT>30% 11.3, 11.9, 9.4, 4.8 Ferritin 501-800, TSAT 20% 11.1, 15.6, 10.8, 5.3 for none, >0-150, >150-300, >350 respectively N/A				12.4, 10.0 12001-25000 23.2, 22.8 >25000 27.5, 25.1 N/A	20.1, 15.3 12001-25000 31.1, 32.5 >25000 30.0, 41.8 N/A	23.2, 22.8 >12 54.9, 61.0 N/A	11.1-12 24.5, 25.0 >12 60.6, 54.1 N/A	
Bailie(49) (2015) N/A DOPPS 2 (2002-2004) 3 (2005-2008) 4 (2009-2011)	0, 1-99, 100-199	200-299, 300-399: 400+:	0: 29.2 (13.7) 1-99: 28.3 (13.1) 100-199: 27.1 (12.1) N/A	200-299: 26.3(11.8) % 300-399: 24.2 (11.7) 400+: 23.5 (11.2) N/A	0: 509 (535) 1-99: 453 (412) 100-199: 430 (380) N/A	200-299: 418 (344) 300-399: 428 (372) 400+: 397 (360) N/A	0: 8.1 (12.2) 1-99: 9.2 (12.8) 100-199: 10.1 (13.2) 1000 units/wk N/A	200-299: 12.2 (14.5) 300-399: 14.7 (16.7) 400: 16.6 (18.8) 1000 units/wk N/A	0: 11.0 (1.6) 1-99: 11.1 (1.6) 100-199: 11.3 (1.5) N/A	200-299: 11.5 (1.4) 300-399: 11.2 (1.5) 400: 11.1 (1.5) N/A	Baseline N/A
Tangri(50) (2015) 2003-2008 DEcIDE	no vs low >0-150mg vs moderate >150-350mg vs high	>350mg per month	Ferritin≤500, TSAT≤20 2.35, 5.08, 21.70, 17.92 Ferritin≤500, TSAT 21-30 1.50, 3.30, 11.41, 5.05 Ferritin 501-800, TSAT≤20 0.24, 0.83, 3.24, 1.30 Ferritin>800 1.38, 2.52, 3.52, 0.91 Ferritin<500, TSAT>30% 0.86, 2.20, 4.52, 1.23 Ferritin 501-800, TSAT 20% 0.66, 1.84, 4.89 1.55 for none, >0-150, >150-300, >350 respectively N/A				≤5000 1.86, 4.53 5000-12000 1.46, 3.54 12000-25000 2.22, 4.43 >25000 1.65, 3.35 N/A	5000 9.37, 2.37 5000-12000 10.63, 3.68 12000-25000 15.43, 8.81 >25000 13.81, 12.86 N/A	<10 0.86, 1.01 10-11 0.91, 1.34 11-12 1.71, 3.62 >12 3.85, 9.81 N/A	<10 2.83, 2.60 10-11 4.45, 3.81 11-12 11.37, 7.53 >12 30.49, 13.80 N/A	Baseline N/A

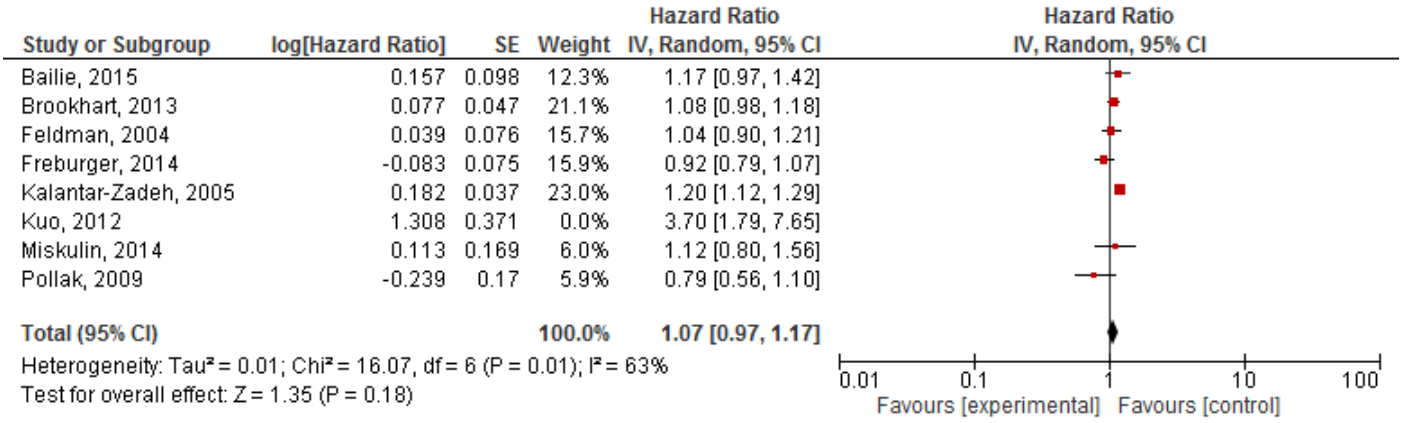
Note: IV = intravenous, TSAT = transferring saturation, ESA = erythropoietin stimulating agent, HGB = hemoglobin, F/U = follow-up, ID = iron dextran, FG = ferric gluconate, IS = iron sucrose, EPO = erythropoietin



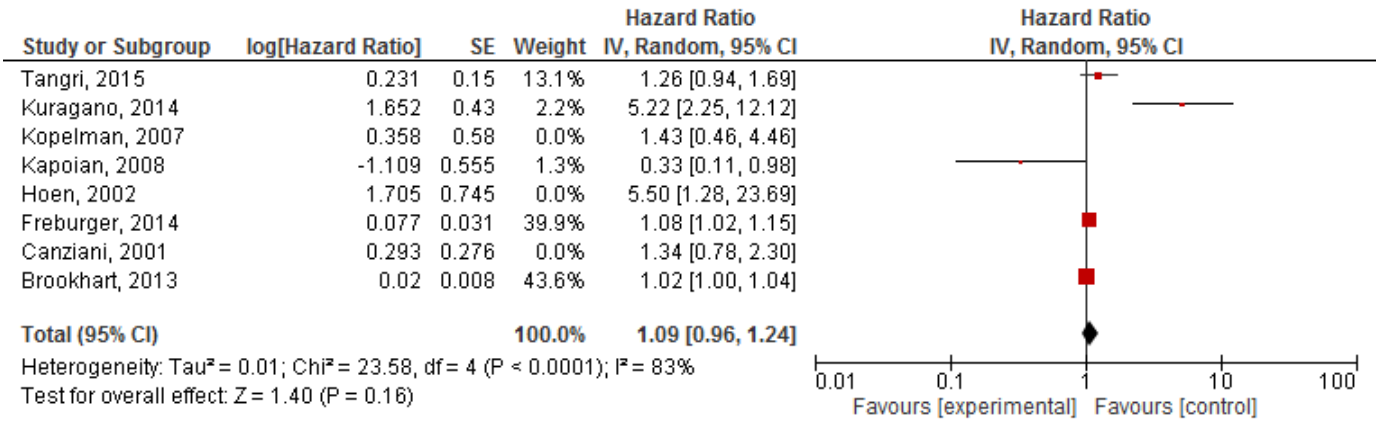
Supplemental Figure 6: Bias Assessment Observational Studies.
Based on the Newcastle-Ottawa Scale for assessing risk of bias in observational studies[25].



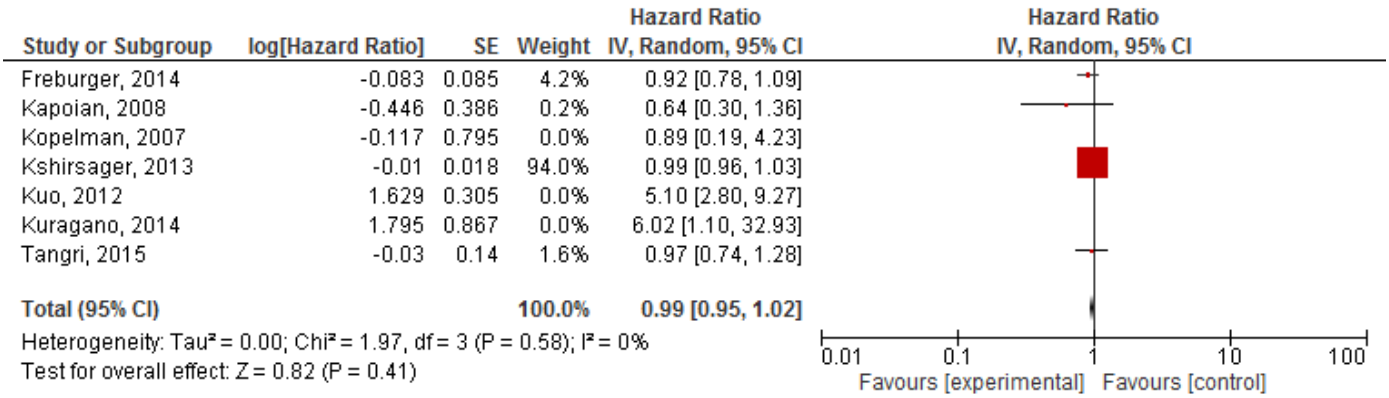
Supplemental Figure 7: Aggregate Risk of Bias Across Included Observational Studies.Based on the Newcastle-Ottawa Scale for assessing risk of bias in observational studies[25].



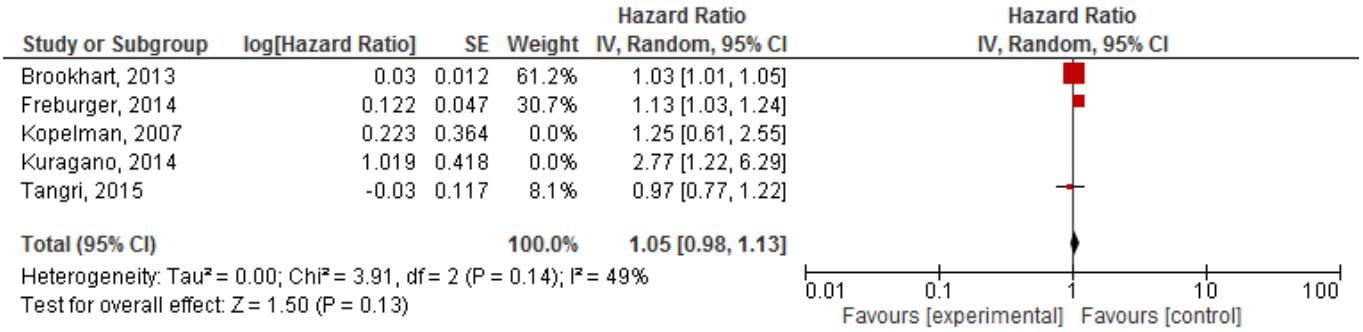
Supplemental Figure 8: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Mortality Events in Observational Studies at Lower Risk of Bias.



Supplemental Figure 9: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Infection Events in Observational Studies at Lower Risk of Bias.



Supplemental Figure 10: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Cardiovascular Events in Observational Studies at Lower Risk of Bias.



Supplemental Figure 11: Sensitivity Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Hospitalization Events in Observational Studies at Lower Risk of Bias.