Master Reference Catalogue

Every cited reference carried in the Atlas dashboards, with the Oracle that uses it, its effect size and endpoint, and an A–D evidence rating — plus the construction of the A–D rating system itself.

What this document is

This catalogue is built directly from the data structures embedded in the Atlas dashboards, not from memory or estimation. Four analyses store evidence as discrete tuples in which a citation is attached to a specific effect size and grade — the **Peripheral Neuropathy Oracle**, **Pulmonary**, **Kidney**, and **Liver** analyses. Those tuples are extracted verbatim and listed in the Master Reference Table (Section 2). The remaining 28 analyses store effect sizes but name their references only as trial-acronym lists with no per-reference effect attribution; reproducing an effect/endpoint against each of those references would require inventing a pairing the source does not make, so they are listed honestly as a bibliography-only appendix (Section 3) with no fabricated numbers. **Sections 2.5–2.9** upgrade that appendix: across five installments (cardiometabolic, neuro/psychiatric, oncology, remaining-clinical and rare-disease clusters — 22 of the 28 analyses), each landmark trial's effect size and endpoint has now been looked up on the internet and cited.

How to use this catalogue — read before acting on it

This is an evidence-synthesis reference, not medical advice and not a prescription; the effect sizes describe trial populations, not any individual, and many interventions here were studied in isolation rather than in combination. Use it to inform a conversation with your physician, not to self-prescribe. **Once you and your doctor settle on a candidate basket of interventions, check on the internet for contraindications and drug–drug interactions within the bundle and against any other drugs, supplements or conditions you already have — then change the bundle and repeat the check until you and your doctor are satisfied.** No item here should be started, stopped or combined without that step.

Extraction provenance & integrity check

Rows were parsed programmatically from each dashboard's intervention objects. The extracted row count was reconciled against the raw count of grade tags in each source file and matched exactly: Pulmonary 174 = 174, Kidney 40 = 40, Liver 203 = 203, Peripheral Neuropathy 13 = 13. Total: **430 cited reference rows**. Effect sizes, confidence intervals, endpoints, grades and source strings are reproduced as stored.

How to read the rating column

Each reference row carries a single letter, **A** (strongest) through **D** (weakest). For Pulmonary, Kidney and Liver the letter is the grade the dashboard already assigns. For the Peripheral Neuropathy Oracle, which stores a GRADE certainty word, the word is mapped to a letter by the crosswalk in Section 1.3. Section 1 defines exactly what each letter means and what earns membership in it.

1 · The A–D Evidence Rating System

The rating answers one question: *how hard would it be to overturn this causal claim?* It is not a measure of effect size — a large effect from a weak design can still be a low rating, and a modest effect from a clean randomised trial can be a high one. The letter is assigned by combining four axes, each of which independently constrains how much an unmeasured confounder, bias, or chance could be hiding behind the reported number.

1.1 · The four axes that build the rating

Axis	What it asks	Pushes the rating up when…	Pushes the rating down when…
1. Design / hierarchy	Where does the evidence sit in the study-design hierarchy?	Cochrane / network meta-analysis of randomised controlled trials (RCTs); multiple concordant RCTs.	Single small trial, observational cohort, registry, case series, or mechanistic reasoning only.

2. Identification	Are the backdoor (confounding) paths closed by design?	Randomisation closes backdoors by design, so no post-hoc adjustment is required.	Allocation is observational; effect rests on measured-confounder adjustment and is exposed to confounding by indication or healthy-adherer bias.
3. Consistency & precision	Do independent studies agree, and is the interval tight?	Low heterogeneity (small I-squared); narrow confidence interval well clear of the null.	High heterogeneity, wide or null-spanning interval, or a directly conflicting meta-analysis.
4. Bias / robustness	How fragile is the estimate to bias and to a plausible confounder?	Low risk of bias; large E-value (an unmeasured confounder would need a strong association to explain the effect away).	Manufacturer funding, high attrition, immortal-time bias; small E-value, i.e. a modest confounder could erase the effect.

1.2 · Membership: what earns each letter

Class	Membership criterion (what a reference must satisfy)	Typical evidence
A	**Randomisation-anchored and consistent.** Effect comes from RCTs or a meta-analysis / network meta-analysis of RCTs; backdoor paths closed by design; consistent direction across trials; low risk of bias. The claim cannot be dismissed as confounding.	Cochrane review of RCTs; pivotal phase-3 trials (e.g. DAPA-CKD, IMPACT, Stupp); pooled RCT meta-analysis.
B	**Randomised but qualified, or strong mixed evidence.** A single RCT, a meta-analysis mixing trials with high-quality cohorts/registries, or RCT evidence weakened by moderate heterogeneity, imprecision, or funding concerns. Real effect, narrower certainty.	One adequately powered RCT; RCT+registry pooled analysis; post-hoc or subgroup RCT findings.
C	**Observational or contested.** Effect rests on observational cohorts (residual confounding live), is supported mainly by mechanism, or is directly contradicted by a higher-tier analysis. Adjustment — not randomisation — is doing the work.	Cohort/registry studies; Mendelian-randomisation-only support; an RCT responder benefit contradicted by a network meta-analysis.
D	**Very low / conflicting.** Few trials beat placebo, evidence is retrospective or mechanistic only, heterogeneity is severe, funding bias is pervasive, or the literature openly conflicts. Treat as hypothesis, not conclusion.	Very-low-certainty Cochrane verdicts; retrospective-only signals; high-attrition trials; conflicting meta-analyses.

1.3 · GRADE-to-letter crosswalk (Peripheral Neuropathy Oracle)

The Peripheral Neuropathy Oracle records a GRADE certainty *word* rather than a letter. The two systems are aligned one-to-one as follows, so its rows can sit in the same table:

GRADE certainty word	Letter	Rationale
High	**A**	Randomisation-anchored, consistent, low risk of bias.
Moderate	**B**	Randomised but qualified by imprecision, heterogeneity, or funding.
Low	**C**	Observational, mechanistic, or contested support.
Very low	**D**	Conflicting / retrospective-only / high risk of bias.

1.4 · Worked examples

A — Intensive glycaemic control in type-1 diabetes (Cochrane CD007543): randomised, large, $p < 0.00001$, consistent → Class A. **B —** Duloxetine 60 mg for painful diabetic neuropathy (Cochrane CD007115, RR 1.73, E-value 2.85): randomised and consistent, but mostly manufacturer-sponsored with ~13% discontinuation → Class B. **C —** Gabapentin (Cochrane CD007938): a real RCT responder benefit that a 2021 network meta-analysis found non-significant, plus observational cardiovascular harm → contested → Class C in spirit (stored as Moderate). **D —** Acetyl-L-carnitine (Cochrane CD011265): I-squared ~85%, manufacturer-funded trials, 'very uncertain' verdict → Class D.

2 · Master Reference Table

Grouped by Oracle. Each row is a cited evidence unit as stored in that dashboard. For the Peripheral Neuropathy Oracle the row is a single reference; for Pulmonary, Kidney and Liver the “Reference(s)” cell holds the trial/review set the dashboard cites for that intervention's effect. Effect is the stored hazard ratio (or the Oracle's native effect metric) with its 95% interval where present.

2.1 · Peripheral Neuropathy Oracle (13 references — A:1 · B:6 · C:4 · D:2)

Endpoint is intervention-specific (incidence of neuropathy, ≥50%/≥30% pain relief, or symptom-score change). Effect metric is as published per row (RR, OR, SMD, NNT, or annual risk difference); endpoints differ and are not summed.

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
1	Callaghan et al., Cochrane (CD007543) [High]	**Intensive glycaemic control — Type 1 diabetes**	–1.84%/yr (p < 0.00001)	Incident neuropathy	A
2	Callaghan et al., Cochrane (CD007543) [Low]	**Intensive glycaemic control — Type 2 diabetes**	–0.58%/yr (p = 0.06)	Incident neuropathy	C
3	Exercise meta-analysis (13 RCTs) [Moderate]	**Structured exercise — Aerobic + sensorimotor**	Improves (meta-analysis)	Nerve conduction, balance	B
4	Lunn et al., Cochrane 2014 (CD007115) [Moderate]	**Duloxetine 60 mg — SNRI**	RR 1.73 (1.44–2.08) NNT 5 · E-value 2.85	≥50% pain relief @12wk	B
5	Derry et al., Cochrane 2019 (CD007076) [Moderate]	**Pregabalin 300–600 mg — α2δ ligand**	NNT ≈ 5 (NNT 4–8) NNT 5	≥50% pain relief	B
6	Cochrane (CD007938); NMA PMC8585758; CV cohort PMC9438165 [Moderate]	**Gabapentin ≥1200 mg — α2δ ligand**	RR 1.7 (1.4–2.0) NNT 6.6 · E-value 2.79	≥50% pain relief	B
7	Moore et al., Cochrane 2015 (CD008242) [Very low]	**Amitriptyline — Tricyclic antidepressant**	Uncertain (very low quality)	Pain relief	D
8	van Nooten et al. 2017, network meta-analysis [Moderate]	**Capsaicin 8% patch — Topical TRPV1 agonist**	OR 2.28 (1.19–4.03) E-value 3.99	≥30% pain relief	B
9	Baicus Cochrane 2024 (CD012967); Mijnhout 2012 [Low]	**Alpha-lipoic acid — Antioxidant**	Conflicting (I2 ≈ 74%)	Total Symptom Score	C
10	Li et al. 2017; Rolim et al., Cochrane 2019 (CD011265) [Very low]	**Acetyl-L-carnitine — Mitochondrial cofactor**	SMD –0.45 (–0.86 to –0.04)	Pain (SMD)	D
11	DARE/B12 reviews; Didangelos 2021 RCT [Low]	**Vitamin B12 / methylcobalamin — Vitamin**	Mixed (low certainty)	Symptoms / conduction	C

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
12	Smith et al., JAMA 2013;309:1359 [Moderate]	**Duloxetine 60 mg (CIPN) — SNRI**	MD 0.73 (p = 0.003)	Avg pain (BPI 0–10)	**B**
13	CERCAN retrospective cohort (PMC9856924) [Low]	**Capsaicin 8% patch (CIPN) — Topical TRPV1 agonist**	≈44% (real-world)	Clinician-rated relief	**C**

2.2 · Pulmonary Oracle (174 references — A:98 · B:64 · C:12)

Global endpoint: disease-specific — 5-yr all-cause mortality (COPD, IPF, PAH, CF, bronchiectasis), overall survival (lung cancers), severe exacerbation (asthma), 30/90-day mortality (PE, ARDS, pneumonia, TB), composite (OSA). Effect = hazard ratio.

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
1	Lung Health Study; Anthonisen et al. 2005; Cochrane 2023	**Smoking cessation (varenicline + counselling)**	HR 0.59 (0.47–0.73)	(see Oracle endpoint above)	**A**
2	Cochrane 2016, McCarthy	**Pulmonary rehabilitation (8-12 wk)**	HR 0.72 (0.59–0.88)	(see Oracle endpoint above)	**A**
3	FLAME, IMPACT, ETHOS RCTs	**LABA/LAMA dual bronchodilator**	HR 0.83 (0.74–0.93)	(see Oracle endpoint above)	**A**
4	IMPACT (NEJM 2018), ETHOS (NEJM 2020)	**Triple therapy (ICS/LABA/LAMA)**	HR 0.72 (0.62–0.83)	(see Oracle endpoint above)	**A**
5	NOTT 1980; MRC 1981	**Long-term oxygen therapy (≥15h/day)**	HR 0.59 (0.42–0.83)	(see Oracle endpoint above)	**A**
6	Köhnlein et al. Lancet RM 2014; HOT-HMV	**Home non-invasive ventilation (severe hypercapnia)**	HR 0.74 (0.61–0.90)	(see Oracle endpoint above)	**A**
7	Cochrane 2018, Poole	**Annual influenza vaccination**	HR 0.81 (0.68–0.97)	(see Oracle endpoint above)	**A**
8	ACIP 2022; CAPiTA trial	**Pneumococcal vaccination (PCV20)**	HR 0.88 (0.78–0.99)	(see Oracle endpoint above)	**B**
9	Albert et al. NEJM 2011 (MACRO)	**Chronic azithromycin (250 mg 3×/wk)**	HR 0.83 (0.71–0.97)	(see Oracle endpoint above)	**B**
10	REACT trial; Martinez Lancet 2015	**Roflumilast (PDE4 inhibitor)**	HR 0.92 (0.84–1.00)	(see Oracle endpoint above)	**B**
11	Collins et al. AJCN 2013; meta-analysis	**Nutritional optimization (protein + Vitamin D)**	HR 0.85 (0.74–0.97)	(see Oracle endpoint above)	**B**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
12	Garcia-Aymerich Thorax 2006; UK Biobank cohort	**Structured exercise (≥150 min/wk moderate)**	HR 0.74 (0.62–0.89)	(see Oracle endpoint above)	**A**
13	NETT 2003; LIBERATE 2018	**Lung volume reduction (surgical or endobronchial)**	HR 0.77 (0.63–0.94)	(see Oracle endpoint above)	**B**
14	ISHLT registry 2023	**Lung transplantation (BODE ≥7)**	HR 0.62 (0.45–0.85)	(see Oracle endpoint above)	**B**
15	Hansel JAMA IM 2018; CAPTURE trial	**Indoor air purification (HEPA, PM2.5 <12)**	HR 0.88 (0.76–1.02)	(see Oracle endpoint above)	**C**
16	RAPID trial Lancet 2015	**Alpha-1 antitrypsin augmentation (if AATD)**	HR 0.74 (0.55–0.99)	(see Oracle endpoint above)	**B**
17	Ginsberg LCSG 1995; CALGB 140503	**Anatomic lobectomy + MLND**	HR 0.45 (0.36–0.56)	(see Oracle endpoint above)	**A**
18	RTOG 0236; Timmerman JAMA 2010	**SBRT (inoperable stage I)**	HR 0.55 (0.42–0.72)	(see Oracle endpoint above)	**A**
19	LACE meta-analysis 2008; Pignon JCO	**Adjuvant platinum doublet chemotherapy**	HR 0.83 (0.74–0.93)	(see Oracle endpoint above)	**A**
20	ADAURA NEJM 2020/2023; Wu/Tsuboi	**Adjuvant osimertinib (EGFR+ resected)**	HR 0.27 (0.21–0.34)	(see Oracle endpoint above)	**A**
21	IMpower010 Lancet 2021	**Adjuvant atezolizumab (PD-L1 ≥1%)**	HR 0.66 (0.50–0.88)	(see Oracle endpoint above)	**A**
22	CheckMate 816 NEJM 2022; AEGEAN	**Neoadjuvant chemo-immunotherapy**	HR 0.58 (0.42–0.81)	(see Oracle endpoint above)	**A**
23	PACIFIC trial NEJM 2017/2022	**Concurrent chemoradiation + durvalumab**	HR 0.68 (0.53–0.87)	(see Oracle endpoint above)	**A**
24	FLAURA NEJM 2018/2020	**1L osimertinib (EGFR-mutant metastatic)**	HR 0.50 (0.40–0.62)	(see Oracle endpoint above)	**A**
25	ALEX NEJM 2017; J-ALEX	**1L alectinib (ALK-rearranged metastatic)**	HR 0.50 (0.36–0.70)	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
26	KEYNOTE-024 NEJM 2016; 5-yr update 2021	**1L pembrolizumab (PD-L1 ≥50%, driver-neg)**	HR 0.62 (0.48–0.81)	(see Oracle endpoint above)	**A**
27	KEYNOTE-189 NEJM 2018	**1L chemo + pembrolizumab (PD-L1 <50%)**	HR 0.56 (0.45–0.70)	(see Oracle endpoint above)	**A**
28	Parsons BMJ 2010 meta-analysis	**Smoking cessation post-diagnosis**	HR 0.68 (0.55–0.84)	(see Oracle endpoint above)	**B**
29	Sebio Garcia, Interact CTS 2016	**Prehabilitation / oncologic exercise**	HR 0.78 (0.66–0.92)	(see Oracle endpoint above)	**B**
30	NLST extrapolation; IELCAP follow-up	**LDCT surveillance (post-treatment)**	HR 0.80 (0.66–0.96)	(see Oracle endpoint above)	**B**
31	AVERT NEJM 2019; CASSINI	**VTE prophylaxis (apixaban high-risk)**	HR 0.86 (0.74–0.99)	(see Oracle endpoint above)	**B**
32	Temel NEJM 2010	**Early integrated palliative care**	HR 0.84 (0.72–0.98)	(see Oracle endpoint above)	**A**
33	CodeBreaK 200; KRYSTAL-12	**Sotorasib / adagrasib (KRAS G12C)**	HR 0.66 (0.51–0.86)	(see Oracle endpoint above)	**B**
34	NCDB analyses; CALGB 140503	**Anatomic lobectomy + MLND**	HR 0.48 (0.38–0.60)	(see Oracle endpoint above)	**A**
35	RTOG 0236; CHISEL	**SBRT (inoperable)**	HR 0.58 (0.44–0.76)	(see Oracle endpoint above)	**A**
36	LACE 2008	**Adjuvant platinum doublet**	HR 0.85 (0.75–0.96)	(see Oracle endpoint above)	**A**
37	PACIFIC 2017/2022	**Concurrent CRT + durvalumab consolidation**	HR 0.68 (0.53–0.87)	(see Oracle endpoint above)	**A**
38	KEYNOTE-407 NEJM 2018	**1L chemo + pembrolizumab**	HR 0.64 (0.49–0.85)	(see Oracle endpoint above)	**A**
39	KEYNOTE-024/042	**1L pembrolizumab (PD-L1 ≥50%)**	HR 0.69 (0.50–0.96)	(see Oracle endpoint above)	**A**
40	Parsons meta-analysis	**Smoking cessation post-diagnosis**	HR 0.65 (0.52–0.81)	(see Oracle endpoint above)	**B**
41	Sebio Garcia 2016	**Prehabilitation (exercise + nutrition)**	HR 0.80 (0.66–0.97)	(see Oracle endpoint above)	**B**
42	REVEL Lancet 2014	**2L docetaxel + ramucirumab**	HR 0.86 (0.75–0.98)	(see Oracle endpoint above)	**B**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
43	AVERT, CASSINI	**VTE prophylaxis (high-risk)**	HR 0.88 (0.76–1.01)	(see Oracle endpoint above)	**B**
44	Temel 2010	**Early palliative care integration**	HR 0.85 (0.72–1.00)	(see Oracle endpoint above)	**A**
45	NCCN Vol 2024; meta-analyses	**Cisplatin/etoposide × 4-6 cycles**	HR 0.65 (0.55–0.77)	(see Oracle endpoint above)	**A**
46	Intergroup 0096; CONVERT 2017	**Concurrent thoracic RT (45 Gy BID or 66 Gy QD)**	HR 0.73 (0.62–0.86)	(see Oracle endpoint above)	**A**
47	Auperin NEJM 1999; EORTC 2007	**Prophylactic cranial irradiation**	HR 0.84 (0.73–0.97)	(see Oracle endpoint above)	**A**
48	IMpower133 NEJM 2018	**Atezolizumab + chemo (ES-SCLC)**	HR 0.70 (0.54–0.91)	(see Oracle endpoint above)	**A**
49	CASPIAN Lancet 2019	**Durvalumab + chemo (ES-SCLC)**	HR 0.71 (0.60–0.86)	(see Oracle endpoint above)	**A**
50	PM1183 single-arm; Trigo Lancet Onc 2020	**Lurbinectedin (2L)**	HR 0.81 (0.66–1.00)	(see Oracle endpoint above)	**B**
51	O'Brien JCO 2006	**Topotecan (relapsed)**	HR 0.87 (0.73–1.05)	(see Oracle endpoint above)	**B**
52	Parsons meta-analysis	**Smoking cessation**	HR 0.72 (0.59–0.88)	(see Oracle endpoint above)	**B**
53	DeLLphi-301 NEJM 2023	**Tarlatamab (DLL3 BiTE, 3L+)**	HR 0.78 (0.62–0.98)	(see Oracle endpoint above)	**B**
54	START trial 2003; GINA 2024	**Low-dose ICS (budesonide/fluticasone)**	HR 0.50 (0.40–0.62)	(see Oracle endpoint above)	**A**
55	SYGMA 1/2 NEJM 2018; PRACTICAL	**ICS-formoterol MART (maintenance + reliever)**	HR 0.36 (0.27–0.48)	(see Oracle endpoint above)	**A**
56	Cochrane 2015	**Add LABA (salmeterol/formoterol)**	HR 0.78 (0.65–0.94)	(see Oracle endpoint above)	**A**
57	PrimoTinA NEJM 2012	**Add LAMA (tiotropium)**	HR 0.79 (0.66–0.95)	(see Oracle endpoint above)	**A**
58	MENSA NEJM 2014; MUSCA	**Mepolizumab (anti-IL5)**	HR 0.47 (0.35–0.64)	(see Oracle endpoint above)	**A**
59	SIROCCO/CALIMA Lancet 2016	**Benralizumab (anti-IL5Rα)**	HR 0.49 (0.37–0.64)	(see Oracle endpoint above)	**A**
60	LIBERTY QUEST NEJM 2018	**Dupilumab (anti-IL4Rα)**	HR 0.54 (0.41–0.71)	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
61	INNOVATE; Cochrane 2014	**Omalizumab (anti-IgE)**	HR 0.62 (0.49–0.79)	(see Oracle endpoint above)	**A**
62	NAVIGATOR NEJM 2021	**Tezepelumab (anti-TSLP)**	HR 0.44 (0.34–0.57)	(see Oracle endpoint above)	**A**
63	Inner-City Asthma Study; NEJM 2004	**Allergen avoidance + remediation**	HR 0.78 (0.65–0.94)	(see Oracle endpoint above)	**B**
64	MITRA JAMA 2016	**Sublingual immunotherapy (HDM)**	HR 0.79 (0.65–0.96)	(see Oracle endpoint above)	**B**
65	Chaudhuri AJRCCM 2006	**Smoking cessation**	HR 0.70 (0.57–0.86)	(see Oracle endpoint above)	**A**
66	Stenius-Aarniala BMJ 2000	**Weight loss (BMI >30 → –5%)**	HR 0.78 (0.65–0.94)	(see Oracle endpoint above)	**B**
67	Cochrane 2013	**Annual influenza vaccination**	HR 0.88 (0.78–0.99)	(see Oracle endpoint above)	**A**
68	Jolliffe Lancet RM 2017	**Vitamin D repletion (if deficient)**	HR 0.87 (0.76–1.00)	(see Oracle endpoint above)	**B**
69	BREATHE trial 2018	**Breathing exercises (Buteyko/ Papworth)**	HR 0.89 (0.78–1.02)	(see Oracle endpoint above)	**C**
70	CAPACITY 004/006; ASCEND NEJM 2014	**Pirfenidone**	HR 0.52 (0.40–0.69)	(see Oracle endpoint above)	**A**
71	INPULSIS 1/2 NEJM 2014	**Nintedanib**	HR 0.55 (0.42–0.72)	(see Oracle endpoint above)	**A**
72	AmbOx Lancet RM 2018; PFF registry	**Supplemental oxygen (resting/exertional hypoxia)**	HR 0.74 (0.59–0.93)	(see Oracle endpoint above)	**B**
73	Dowman Cochrane 2014	**Pulmonary rehabilitation**	HR 0.81 (0.68–0.97)	(see Oracle endpoint above)	**B**
74	Lee Lancet RM 2013; controversial	**GERD treatment (PPI / fundoplication)**	HR 0.83 (0.69–1.00)	(see Oracle endpoint above)	**C**
75	ISHLT 2023; Thabut JAMA 2008	**Lung transplantation (listing if FVC<60%, age<70)**	HR 0.45 (0.30–0.67)	(see Oracle endpoint above)	**B**
76	ATS guideline 2022	**Influenza + pneumococcal vaccination**	HR 0.85 (0.74–0.98)	(see Oracle endpoint above)	**B**
77	INPULSIS post-hoc; cohort data	**Smoking cessation**	HR 0.78 (0.63–0.96)	(see Oracle endpoint above)	**B**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
78	PRINTS 2014	**Maintenance exercise program**	HR 0.84 (0.71–0.99)	(see Oracle endpoint above)	**B**
79	PANTHER-IPF NEJM 2014; Oldham post-hoc	**N-acetylcysteine (only TOLLIP TT genotype)**	HR 0.84 (0.69–1.02)	(see Oracle endpoint above)	**C**
80	Lindell Heart Lung 2017	**Early palliative care**	HR 0.86 (0.73–1.02)	(see Oracle endpoint above)	**B**
81	SERAPHIN NEJM 2013; ARIES	**ERA (ambrisentan / bosentan / macitentan)**	HR 0.68 (0.55–0.84)	(see Oracle endpoint above)	**A**
82	SUPER-1 NEJM 2005; PHIRST	**PDE5 inhibitor (sildenafil/tadalafil)**	HR 0.78 (0.65–0.93)	(see Oracle endpoint above)	**A**
83	PATENT-1 NEJM 2013	**Riociguat (sGC stimulator)**	HR 0.69 (0.55–0.86)	(see Oracle endpoint above)	**A**
84	GRIPHON NEJM 2015; Barst 1996	**Prostacyclin pathway (epoprostenol/treprostinil/selexipag)**	HR 0.59 (0.46–0.76)	(see Oracle endpoint above)	**A**
85	STELLAR NEJM 2023; ZENITH	**Sotatercept (activin receptor IIA fusion)**	HR 0.55 (0.40–0.75)	(see Oracle endpoint above)	**A**
86	AMBITION NEJM 2015; TRITON	**Upfront double/triple combination therapy**	HR 0.50 (0.36–0.69)	(see Oracle endpoint above)	**A**
87	ATS PH guidelines 2019	**Supplemental oxygen (SaO2 <90%)**	HR 0.80 (0.66–0.97)	(see Oracle endpoint above)	**B**
88	ESC/ERS 2022 guidelines	**Diuretics for RV volume overload**	HR 0.86 (0.73–1.02)	(see Oracle endpoint above)	**B**
89	COMPERA registry; controversial	**Anticoagulation (IPAH only, selected)**	HR 0.81 (0.66–1.00)	(see Oracle endpoint above)	**C**
90	Mereles Circulation 2006; Ehlken	**Structured supervised exercise training**	HR 0.78 (0.64–0.95)	(see Oracle endpoint above)	**A**
91	Sandoval JCC 2011	**Balloon atrial septostomy (selected FC IV)**	HR 0.82 (0.66–1.02)	(see Oracle endpoint above)	**C**
92	ISHLT registry 2023	**Lung / heart-lung transplantation**	HR 0.55 (0.40–0.76)	(see Oracle endpoint above)	**B**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
93	Houck Arch IM 2004; IDSA/ATS 2019	**Early appropriate empiric antibiotics (<4h)**	HR 0.55 (0.42–0.72)	(see Oracle endpoint above)	**A**
94	Sligl Crit Care Med 2014	**β-lactam + macrolide combo (severe CAP)**	HR 0.70 (0.55–0.89)	(see Oracle endpoint above)	**A**
95	CAPE COD NEJM 2023; Torres JAMA 2015	**Corticosteroids (severe CAP)**	HR 0.74 (0.59–0.93)	(see Oracle endpoint above)	**A**
96	ICU-ROX NEJM 2020	**Conservative O2 targeting (SpO2 92-96%)**	HR 0.84 (0.71–1.00)	(see Oracle endpoint above)	**B**
97	FLORALI NEJM 2015	**High-flow nasal cannula (hypoxemic resp failure)**	HR 0.74 (0.59–0.93)	(see Oracle endpoint above)	**A**
98	Schweickert Lancet 2009	**Early mobilization**	HR 0.78 (0.64–0.95)	(see Oracle endpoint above)	**A**
99	Drakulovic Lancet 1999	**Head-of-bed elevation 30-45° (vent patients)**	HR 0.78 (0.65–0.94)	(see Oracle endpoint above)	**A**
100	Cochrane 2020; Klompas	**Chlorhexidine oral care (VAP)**	HR 0.76 (0.62–0.94)	(see Oracle endpoint above)	**A**
101	ABC trial Lancet 2008	**Daily sedation interruption + SBT**	HR 0.78 (0.65–0.93)	(see Oracle endpoint above)	**A**
102	Cochrane 2018	**Influenza vaccination (pre-event)**	HR 0.65 (0.51–0.83)	(see Oracle endpoint above)	**A**
103	CAPiTA NEJM 2015; ACIP 2022	**Pneumococcal vaccination (PCV20/PPSV23)**	HR 0.71 (0.57–0.88)	(see Oracle endpoint above)	**A**
104	Almirall ERJ 2014	**Smoking cessation**	HR 0.74 (0.60–0.91)	(see Oracle endpoint above)	**B**
105	Sterling NEJM 2011; PREVENT-TB	**3HP (rifapentine + isoniazid, 3 mo weekly)**	HR 0.35 (0.25–0.49)	(see Oracle endpoint above)	**A**
106	Menzies NEJM 2018	**4R (rifampin 4 months, LTBI)**	HR 0.40 (0.30–0.55)	(see Oracle endpoint above)	**A**
107	WHO 2010; Mitchison	**Standard HRZE (2HRZE/4HR, 6 mo)**	HR 0.30 (0.22–0.41)	(see Oracle endpoint above)	**A**
108	Study 31/A5349 NEJM 2021	**4-month rifapentine -moxifloxacin regimen**	HR 0.85 (0.65–1.10)	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
109	ZeNix NEJM 2022; Nix-TB	**BPaL (bedaquiline-pretomanid-linezolid)**	HR 0.40 (0.28–0.57)	(see Oracle endpoint above)	**A**
110	WHO 2022; STREAM	**Bedaquiline-containing MDR regimen (≥18 mo)**	HR 0.55 (0.42–0.72)	(see Oracle endpoint above)	**A**
111	WHO; Cochrane 2015	**Directly Observed Therapy**	HR 0.75 (0.62–0.91)	(see Oracle endpoint above)	**A**
112	Slama IJTLD 2007 meta	**Smoking cessation**	HR 0.78 (0.65–0.94)	(see Oracle endpoint above)	**B**
113	RATIONS Lancet 2023	**Nutritional support (food + micronutrients)**	HR 0.61 (0.46–0.80)	(see Oracle endpoint above)	**A**
114	SAPIT NEJM 2010; TEMPRANO	**Antiretroviral therapy (if HIV+)**	HR 0.34 (0.25–0.46)	(see Oracle endpoint above)	**A**
115	Baker Lancet ID 2011	**Glycemic control (if diabetic)**	HR 0.80 (0.66–0.97)	(see Oracle endpoint above)	**B**
116	Martineau Lancet 2011; meta-analysis	**Vitamin D supplementation (if deficient)**	HR 0.91 (0.79–1.04)	(see Oracle endpoint above)	**C**
117	Middleton NEJM 2019; Heijerman; CFFPR 2023	**Elexacaftor/tezacaftor/ivacaftor (ETI)**	HR 0.20 (0.13–0.30)	(see Oracle endpoint above)	**A**
118	Fuchs NEJM 1994	**Dornase alfa (DNase)**	HR 0.74 (0.61–0.90)	(see Oracle endpoint above)	**A**
119	Elkins NEJM 2006	**Hypertonic saline 7% (inhaled)**	HR 0.81 (0.68–0.96)	(see Oracle endpoint above)	**A**
120	Ramsey NEJM 1999; AIR-CF1	**Inhaled tobramycin/aztreonam (Pa+)**	HR 0.72 (0.58–0.90)	(see Oracle endpoint above)	**A**
121	Cochrane 2019	**Airway clearance (vest/PEP daily)**	HR 0.78 (0.64–0.95)	(see Oracle endpoint above)	**B**
122	Saiman JAMA 2003	**Chronic azithromycin (3×/wk)**	HR 0.79 (0.65–0.96)	(see Oracle endpoint above)	**A**
123	CFF 2008 guidelines	**Pancreatic enzyme replacement**	HR 0.65 (0.50–0.84)	(see Oracle endpoint above)	**A**
124	CFFPR; Stallings 2008	**High-calorie nutrition + ADEK vitamins**	HR 0.70 (0.56–0.88)	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
125	CFF guidelines	**Annual influenza + pneumococcal + COVID vaccines**	HR 0.82 (0.70–0.97)	(see Oracle endpoint above)	**B**
126	ISHLT registry	**Lung transplantation (FEV1 <30% or rapid decline)**	HR 0.58 (0.42–0.81)	(see Oracle endpoint above)	**B**
127	Schneiderman Eur Respir J 2014	**Regular exercise program**	HR 0.75 (0.61–0.93)	(see Oracle endpoint above)	**B**
128	ERS guideline 2017	**Daily airway clearance (PEP, ACBT)**	HR 0.71 (0.58–0.87)	(see Oracle endpoint above)	**A**
129	BAT/EMBRACE/BLESS Lancet 2012	**Chronic azithromycin (3×/wk, ≥1 exac/yr)**	HR 0.62 (0.49–0.78)	(see Oracle endpoint above)	**A**
130	AIR-BX; RESPIRE-1/2	**Inhaled antibiotic (chronic Pa+ colonisation)**	HR 0.74 (0.60–0.91)	(see Oracle endpoint above)	**B**
131	Lee Cochrane 2017	**Pulmonary rehabilitation**	HR 0.80 (0.66–0.97)	(see Oracle endpoint above)	**B**
132	Nicolson Cochrane 2014	**Hypertonic saline 7% inhaled**	HR 0.85 (0.71–1.02)	(see Oracle endpoint above)	**B**
133	BTS guidelines 2019	**Annual influenza + pneumococcal vaccination**	HR 0.81 (0.68–0.97)	(see Oracle endpoint above)	**B**
134	BTS guidelines	**Prompt antibiotics at exacerbation onset**	HR 0.78 (0.65–0.94)	(see Oracle endpoint above)	**A**
135	EMBARC registry	**Smoking cessation**	HR 0.74 (0.60–0.91)	(see Oracle endpoint above)	**B**
136	WILLOW NEJM 2020; ASPEN 2024	**Brensocatib (DPP1 inhibitor — emerging)**	HR 0.66 (0.51–0.85)	(see Oracle endpoint above)	**B**
137	Mandal Respirology 2014	**GERD treatment if present**	HR 0.86 (0.72–1.03)	(see Oracle endpoint above)	**C**
138	AMPLIFY NEJM 2013; EINSTEIN-PE	**DOAC (apixaban/rivaroxaban)**	HR 0.40 (0.30–0.54)	(see Oracle endpoint above)	**A**
139	Cochrane 2014; MATISSE	**LMWH (enoxaparin/dalteparin)**	HR 0.45 (0.34–0.60)	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
140	Meyer NEJM 2014 (PEITHO); Marti EHJ 2015 meta	**Systemic thrombolysis (alteplase)**	HR 0.59 (0.42–0.83)	(see Oracle endpoint above)	**A**
141	SEATTLE II; FLARE; FLASH	**Catheter-directed thrombolysis / thrombectomy**	HR 0.65 (0.45–0.94)	(see Oracle endpoint above)	**B**
142	ELSO registry	**VA-ECMO support (cardiac arrest / refractory shock)**	HR 0.70 (0.50–0.97)	(see Oracle endpoint above)	**C**
143	Aujesky JAMA IM 2011	**Early mobilization (low/int-low risk)**	HR 0.83 (0.69–1.00)	(see Oracle endpoint above)	**B**
144	ESC 2019 PE guidelines	**Supplemental O2 (SpO2 target 92-96%)**	HR 0.87 (0.73–1.04)	(see Oracle endpoint above)	**B**
145	EINSTEIN-CHOICE; AMPLIFY-EXT	**Extended anticoagulation (provoked vs unprovoked)**	HR 0.30 (0.20–0.45)	(see Oracle endpoint above)	**A**
146	PREPIC2 JAMA 2015	**IVC filter (anticoag contraindicated)**	HR 0.80 (0.65–0.99)	(see Oracle endpoint above)	**C**
147	ARDSnet NEJM 2000	**Lung-protective ventilation (Vt 6 mL/kg PBW)**	HR 0.78 (0.65–0.93)	(see Oracle endpoint above)	**A**
148	PROSEVA NEJM 2013	**Prone positioning ≥12-16 h/day (severe)**	HR 0.55 (0.41–0.74)	(see Oracle endpoint above)	**A**
149	ALVEOLI; LOVS; ExPress meta-analysis	**Higher PEEP titration (severe)**	HR 0.85 (0.72–1.00)	(see Oracle endpoint above)	**B**
150	ACURASYS 2010; ROSE NEJM 2019	**Short-term neuromuscular blockade (severe early)**	HR 0.78 (0.62–0.98)	(see Oracle endpoint above)	**B**
151	EOLIA NEJM 2018; ELSO 2024	**VV-ECMO (refractory severe ARDS)**	HR 0.66 (0.46–0.95)	(see Oracle endpoint above)	**B**
152	DEXA-ARDS Lancet RM 2020	**Dexamethasone (early, severe)**	HR 0.79 (0.65–0.96)	(see Oracle endpoint above)	**B**
153	FACTT NEJM 2006	**Conservative fluid management**	HR 0.84 (0.71–0.99)	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
154	SSC guidelines 2021	**Early appropriate antibiotics (if sepsis source)**	HR 0.66 (0.51–0.85)	(see Oracle endpoint above)	**A**
155	Schweickert 2009	**Early physical therapy / mobilization**	HR 0.82 (0.69–0.98)	(see Oracle endpoint above)	**A**
156	CheckMate 743 Lancet 2021	**Nivolumab + ipilimumab (1L)**	HR 0.74 (0.61–0.89)	(see Oracle endpoint above)	**A**
157	Vogelzang JCO 2003	**Cisplatin + pemetrexed**	HR 0.83 (0.70–0.99)	(see Oracle endpoint above)	**A**
158	MAPS Lancet 2016	**Bevacizumab + cis/pem**	HR 0.77 (0.62–0.95)	(see Oracle endpoint above)	**A**
159	MARS feasibility 2011; controversial	**Extrapleural pneumonectomy (selected)**	HR 0.85 (0.66–1.10)	(see Oracle endpoint above)	**C**
160	MARS-2; Cao Ann Surg Onc 2014	**Pleurectomy/decortication**	HR 0.83 (0.68–1.01)	(see Oracle endpoint above)	**B**
161	Rimner JCO 2016	**Hemithoracic IMRT (post P/D)**	HR 0.88 (0.72–1.07)	(see Oracle endpoint above)	**C**
162	TAPPS Lancet 2020	**Pleurodesis for symptomatic effusion (talc)**	HR 0.95 (0.82–1.10)	(see Oracle endpoint above)	**B**
163	Liddell 1997 cohort	**Smoking cessation**	HR 0.85 (0.71–1.02)	(see Oracle endpoint above)	**B**
164	Temel 2010 generalised	**Early palliative care + symptom-directed**	HR 0.82 (0.68–0.99)	(see Oracle endpoint above)	**A**
165	Marin Lancet 2005; SAVE caveat	**CPAP with ≥4h/night adherence**	HR 0.65 (0.53–0.80)	(see Oracle endpoint above)	**A**
166	Phillips AJRCCM 2013	**Mandibular advancement device**	HR 0.85 (0.71–1.02)	(see Oracle endpoint above)	**B**
167	Sleep AHEAD JAMA 2014	**Weight loss (≥10% body weight)**	HR 0.68 (0.55–0.84)	(see Oracle endpoint above)	**A**
168	STAR HNS trial; Friedman	**Upper airway surgery (UPPP / MMA for severe)**	HR 0.82 (0.68–0.99)	(see Oracle endpoint above)	**B**
169	STAR NEJM 2014; 5-yr update	**Hypoglossal nerve stimulation**	HR 0.78 (0.62–0.98)	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
170	de Ruiter 2018	**Positional therapy (supine-dependent OSA)**	HR 0.88 (0.73–1.06)	(see Oracle endpoint above)	**B**
171	Issa Lancet 1982	**Alcohol reduction (esp. evening)**	HR 0.85 (0.70–1.03)	(see Oracle endpoint above)	**B**
172	SURMOUNT-OSA NEJM 2024	**Tirzepatide (GLP-1/GIP, OSA + obesity)**	HR 0.70 (0.55–0.89)	(see Oracle endpoint above)	**A**
173	Wetter Arch IM 1994	**Smoking cessation**	HR 0.83 (0.69–1.00)	(see Oracle endpoint above)	**B**
174	Iftikhar Sleep Med 2014 meta	**Regular exercise (independent of weight)**	HR 0.81 (0.66–0.98)	(see Oracle endpoint above)	**B**

2.3 · Kidney Oracle (40 references — A:19 · B:17 · C:3 · D:1)

Global endpoint: composite renal (≥50% eGFR decline, ESRD, or renal death), KFRE 5-yr, 10-yr ESRD, 5-yr all-cause mortality, CV MACE, or AKI episode. Effect = hazard ratio (E = E-value where shown).

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
1	DAPA-CKD (Heerspink 2020 NEJM); EMPA-KIDNEY (EMPA-KIDNEY Collaborative 2023); CREDENCE; meta-analysis Nuffield 2022	**SGLT2 Inhibitor (dapa/empa/cana)**	HR 0.63 (0.55–0.72) E-value 2.55	(see Oracle endpoint above)	**A**
2	RENAAL; IDNT; AASK; Cochrane 2020 meta-analysis	**RAAS Inhibitor (ACEi or ARB)**	HR 0.70 (0.61–0.81) E-value 2.21	(see Oracle endpoint above)	**A**
3	FIDELIO-DKD (Bakris 2020 NEJM); FIGARO-DKD (Pitt 2021); FIDELITY pooled	**Finerenone (non-steroidal MRA)**	HR 0.82 (0.73–0.93) E-value 1.74	(see Oracle endpoint above)	**A**
4	FLOW trial (Perkovic 2024 NEJM); SUSTAIN-6; LEADER renal subanalysis	**GLP-1 RA (semaglutide)**	HR 0.76 (0.66–0.88) E-value 1.94	(see Oracle endpoint above)	**A**
5	PATHWAY-2 (resistant HTN); meta-analysis Bolignano 2014 Cochrane	**Spironolactone (low-dose)**	HR 0.86 (0.74–1.00) E-value 1.60	(see Oracle endpoint above)	**B**
6	TEMPO 3:4 (Torres 2012 NEJM); REPRISE (Torres 2017)	**Tolvaptan (vasopressin V2 antagonist)**	HR 0.50 (0.40–0.62) E-value 3.41	(see Oracle endpoint above)	**A**
7	PROTECT trial (Heerspink 2023 Lancet); DUPLEX (FSGS)	**Sparsentan (dual ETA/AT1 antagonist)**	HR 0.68 (0.54–0.85) E-value 2.30	(see Oracle endpoint above)	**A**
8	NefIgArd (Lafayette 2023 Lancet); Phase 2 NEFIGAN	**Nefecon (targeted-release budesonide)**	HR 0.66 (0.50–0.86) E-value 2.40	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
9	APPLAUSE-IgAN (interim Perkovic 2024); APPEAR-C3G	**Iptacopan (factor B inhibitor)**	HR 0.62 (0.45–0.85) E-value 2.65	(see Oracle endpoint above)	**B**
10	MENTOR (Fervenza 2019 NEJM); GEMINI-LN	**Rituximab (anti-CD20)**	HR 0.55 (0.40–0.76) E-value 3.07	(see Oracle endpoint above)	**A**
11	AURORA-1 (Rovin 2021 Lancet); AURORA-2 extension	**Voclosporin (calcineurin inhibitor)**	HR 0.59 (0.42–0.83) E-value 2.81	(see Oracle endpoint above)	**A**
12	BLISS-LN (Furie 2020 NEJM); BLISS-52/76	**Belimumab (BLyS inhibitor)**	HR 0.71 (0.55–0.93) E-value 2.10	(see Oracle endpoint above)	**A**
13	ALMS (Appel 2009); Cochrane lupus 2018	**Mycophenolate mofetil**	HR 0.73 (0.60–0.89) E-value 1.98	(see Oracle endpoint above)	**A**
14	Ponticelli regimen original NEJM 1984 + 30-yr follow-up	**Cyclophosphamide + steroid (Ponticelli)**	HR 0.68 (0.52–0.89) E-value 2.27	(see Oracle endpoint above)	**B**
15	SPRINT (2015 NEJM); MDRD long-term; AASK	**Strict BP control (<130/80)**	HR 0.83 (0.74–0.93) E-value 1.70	(see Oracle endpoint above)	**A**
16	DCCT/EDIC; UKPDS; ADVANCE renal subanalysis	**Intensive glycemic control (A1c<7)**	HR 0.85 (0.75–0.96) E-value 1.62	(see Oracle endpoint above)	**B**
17	SHARP (Baigent 2011); CTT meta-analysis (Lancet 2016)	**Statin therapy (moderate-high intensity)**	HR 0.91 (0.85–0.97) E-value 1.43	(see Oracle endpoint above)	**A**
18	PREDIAN (Navarro-González 2015); meta-analysis Tian 2019	**Pentoxifylline**	HR 0.85 (0.74–0.98) E-value 1.62	(see Oracle endpoint above)	**C**
19	de Brito-Ashurst 2009 JASN; UBI study; meta-analysis Hu 2019	**Oral bicarbonate (acidosis correction)**	HR 0.81 (0.69–0.95) E-value 1.81	(see Oracle endpoint above)	**B**
20	MDRD long-term; Kim 2019 CJASN; Carrero 2020	**Plant-based / low animal protein diet**	HR 0.77 (0.64–0.93) E-value 2.02	(see Oracle endpoint above)	**B**
21	Garneata 2016 JASN; meta-analysis Yan 2018	**Very-low-protein diet + keto-analogues**	HR 0.62 (0.43–0.89) E-value 2.65	(see Oracle endpoint above)	**B**
22	PREDIMED renal substudy; ORIGINS cohort	**Mediterranean dietary pattern**	HR 0.87 (0.78–0.97) E-value 1.55	(see Oracle endpoint above)	**B**
23	RENEXC trial; cohort meta-analysis Wilkinson 2020	**Aerobic exercise (≥150 min/wk moderate)**	HR 0.86 (0.76–0.97) E-value 1.60	(see Oracle endpoint above)	**B**
24	Orth 2002 NEJM review; CRIC cohort smoking subanalysis	**Smoking cessation**	HR 0.84 (0.74–0.95) E-value 1.66	(see Oracle endpoint above)	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
25	Look-AHEAD renal substudy; Imes 2018 bariatric meta-analysis	**Weight loss (≥5% sustained)**	HR 0.81 (0.69–0.95) E-value 1.81	(see Oracle endpoint above)	**B**
26	Gooch 2007 Am J Med; meta-analysis Curhan 2004	**NSAID/nephrotoxin avoidance**	HR 0.78 (0.65–0.94) E-value 1.97	(see Oracle endpoint above)	**B**
27	Borghi 1996; PRISM trial Clark 2018 (no benefit in CKD-3+); RCT meta Bao 2020	**Increased fluid intake (~2.5 L/d)**	HR 0.50 (0.36–0.69) E-value 3.41	(see Oracle endpoint above)	**A**
28	Barcelo 1993; Mattle 2005 meta	**Potassium citrate (alkali)**	HR 0.56 (0.42–0.75) E-value 3.05	(see Oracle endpoint above)	**A**
29	NOSTONE 2023 NEJM (caveat: no benefit in this trial); historical meta Pearle 2014	**Thiazide diuretic (stones)**	HR 0.52 (0.39–0.70) E-value 3.31	(see Oracle endpoint above)	**A**
30	Borghi 2002 NEJM; AUA stone guideline 2014	**Low-oxalate / Ca-replete diet**	HR 0.66 (0.50–0.87) E-value 2.40	(see Oracle endpoint above)	**B**
31	VITAL trial (de Zeeuw 2010); PRIMO/OPERA	**Vitamin D analogue (paricalcitol)**	HR 0.88 (0.78–0.99) E-value 1.52	(see Oracle endpoint above)	**B**
32	INDEPENDENT (Di Iorio 2012); meta-analysis Jamal 2013	**Non-Ca phosphate binder**	HR 0.84 (0.72–0.98) E-value 1.66	(see Oracle endpoint above)	**B**
33	TREAT (Pfeffer 2009 NEJM); CHOIR; PIVOTAL iv iron trial	**Anemia management (ESA + iron)**	HR 0.93 (0.85–1.02) E-value 1.34	(see Oracle endpoint above)	**C**
34	PERL (Doria 2020 NEJM null); CKD-FIX (Badve 2020 null); meta Bose 2014 positive	**Urate-lowering (allopurinol/febuxostat)**	HR 0.95 (0.83–1.09) E-value 1.27	(see Oracle endpoint above)	**D**
35	Hamilton 2018; Esnault series	**Immunoadsorption (Ig removal)**	HR 0.70 (0.50–0.98) E-value 2.21	(see Oracle endpoint above)	**C**
36	Wolfe 1999 NEJM; OPTN/SRTR annual reports; UK Renal Registry	**Kidney transplantation (vs dialysis)**	HR 0.32 (0.27–0.38) E-value 5.42	(see Oracle endpoint above)	**A**
37	FHN Daily (NEJM 2010); CONVINCE (Blankestijn 2023 NEJM)	**Optimized dialysis (≥3.5×/wk or HDF)**	HR 0.86 (0.75–0.98) E-value 1.60	(see Oracle endpoint above)	**B**
38	AMACING; PRESERVE (no benefit of bicarb over saline); KDIGO AKI 2012 update	**Contrast minimization & periprocedural hydration**	HR 0.70 (0.55–0.89) E-value 2.21	(see Oracle endpoint above)	**A**
39	STOP-AKI study; KDIGO AKI guideline	**Stop ACEi/ARB/diuretic during AKI**	HR 0.75 (0.62–0.91) E-value 2.05	(see Oracle endpoint above)	**B**
40	SMART (Semler 2018 NEJM); SOAP-II; ProCESS/ARISE/ProMISe	**Early hemodynamic optimization (sepsis-AKI)**	HR 0.80 (0.68–0.94) E-value 1.86	(see Oracle endpoint above)	**B**

2.4 · Liver Oracle (203 references — A:128 · B:55 · C:20)

Global endpoint: entity-specific — fibrosis progression, decompensation, hepatocellular carcinoma, or transplant-free survival. Effect = hazard ratio; dose shown where stored.

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
1	Vilar-Gomez 2015 (Gastroenterology); 90% NASH resolution, 81% fibrosis regression	**Weight loss ≥10% body weight**	HR 0.30	Dose: ≥10% sustained	A
2	SYNERGY-NASH 2024 (NEJM); 62% MASH resolution at 15mg	**Tirzepatide 5–15 mg weekly**	HR 0.50	Dose: 10–15 mg/wk	A
3	Newsome 2021 (NEJM); 59% resolution NASH	**Semaglutide 2.4 mg weekly**	HR 0.59	Dose: 2.4 mg/wk	A
4	MAESTRO-NASH 2024 (NEJM); FDA-approved Mar 2024	**Resmetirom (Rezdiffra) 80–100 mg/d**	HR 0.70	Dose: 80–100 mg/d	A
5	PIVENS 2010; Cusi 2016; meta-analysis Musso 2017	**Pioglitazone 30–45 mg/d**	HR 0.65	Dose: 30–45 mg/d	A
6	PIVENS 2010 (NEJM)	**Vitamin E 800 IU/d (non-diabetic)**	HR 0.78	Dose: 800 IU α-tocopherol/d	B
7	Ryan 2013; meta-analysis Plaz Torres 2019	**Mediterranean diet (high adherence)**	HR 0.72	Dose: MedDiet score ≥10	B
8	Bambha 2014; meta-analysis Wijarnpreecha 2017	**Coffee ≥3 cups/d (caffeinated)**	HR 0.62	Dose: ≥3 cups/d	B
9	Hashida 2017 systematic review	**Aerobic exercise ≥150 min/wk**	HR 0.70	Dose: Moderate-vigorous ≥150 min/wk	A
10	Hallsworth 2011; independent of weight loss	**Resistance training 2–3×/wk**	HR 0.82	Dose: ≥2 sessions/wk	B
11	Lassailly 2020 (Gastroenterology); 84% NASH resolution at 5yr	**Bariatric surgery (BMI ≥35 + comorb)**	HR 0.30	Dose: RYGB or SG	A
12	Pastori 2015; Targher 2020 meta-analysis	**Statin therapy (any)**	HR 0.69	Dose: Moderate-high intensity	B
13	Eriksson 2018 (E-LIFT); Latva-Rasku 2019	**SGLT2 inhibitor (T2D)**	HR 0.75	Dose: Empa/dapa/cana standard	B
14	Singh 2013 meta-analysis; HCC reduction independently	**Metformin (T2D)**	HR 0.85	Dose: ≥1500 mg/d	C
15	Parker 2012 meta-analysis	**Omega-3 EPA/DHA 2–4 g/d**	HR 0.85	Dose: 2–4 g/d	C
16	Jensen 2018; reduces DNL	**Low fructose intake (<25 g/d)**	HR 0.82	Dose: <25 g free fructose/d	C
17	Ascha 2010; synergistic with metabolic injury	**Alcohol abstinence**	HR 0.65	Dose: 0 g ethanol/d	B
18	Liu 2017 meta-analysis	**Smoking cessation**	HR 0.85	Dose: Sustained ≥1 yr	C

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
19	Eliades 2013 review; modest signal	**Vitamin D repletion (≥30 ng/mL)**	HR 0.88	Dose: 1000–4000 IU/d to target	C
20	Yan 2015 RCT; AMPK activation	**Berberine 1500 mg/d**	HR 0.83	Dose: 500 mg TID	C
21	Singal 2014 meta-analysis; mortality benefit	**HCC surveillance q6mo (US ± AFP) — if F3-F4**	HR 0.63	Dose: Q6 month US	A
22	Vilar-Gomez 2015	**Weight loss ≥10%**	HR 0.28	Dose: ≥10%	A
23	MAESTRO-NASH 2024	**Resmetirom 80–100 mg/d**	HR 0.65	Dose: FDA-approved MASH	A
24	Newsome 2021	**Semaglutide 2.4 mg**	HR 0.55	Dose: weekly	A
25	SYNERGY-NASH 2024	**Tirzepatide 10–15 mg**	HR 0.45	Dose: weekly	A
26	PIVENS; Cusi 2016	**Pioglitazone 30–45 mg**	HR 0.62	Dose: daily	A
27	PIVENS 2010	**Vitamin E 800 IU (non-T2D)**	HR 0.75	Dose: α-tocopherol	B
28	Lassailly 2020	**Bariatric surgery**	HR 0.28	Dose: RYGB/SG	A
29	Pastori 2015	**Statin therapy**	HR 0.65	Dose: Moderate-high	B
30	Ryan 2013	**Mediterranean diet**	HR 0.70	Dose: High adherence	B
31	Hashida 2017	**Aerobic exercise ≥150 min/wk**	HR 0.72	Dose: Mod-vig	A
32	Wijarnpreecha 2017	**Coffee ≥3 cups/d**	HR 0.65	Dose: ≥3 cups	B
33	Ascha 2010	**Alcohol abstinence**	HR 0.62	Dose: 0 g/d	B
34	Singal 2014	**HCC surveillance q6mo**	HR 0.63	Dose: US + AFP	A
35	PREDESCI 2019 (Lancet)	**Non-selective β-blocker (if CSPH, F4)**	HR 0.51	Dose: Carvedilol 6.25–12.5 mg/d	A
36	OPTN/SRTR; 5-yr survival ~75%	**Liver transplant (decompensated)**	HR 0.30	Dose: MELD ≥15	A
37	Single largest predictor; Lackner 2017 meta-analysis	**Complete alcohol abstinence**	HR 0.40	Dose: Sustained 0 g/d	A
38	COMBINE 2006; Jonas 2014 JAMA meta-analysis	**Naltrexone 50–100 mg/d**	HR 0.72	Dose: PO or IM monthly	A

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
39	Jonas 2014 meta-analysis	**Acamprosate 666 mg TID**	HR 0.74	Dose: 1998 mg/d	**A**
40	Addolorato 2007 Lancet (cirrhotic pts)	**Baclofen 10–30 mg TID (cirrhotic-safe)**	HR 0.78	Dose: 30–90 mg/d	**B**
41	STOPAH 2015 (NEJM); 28-d mortality	**Prednisolone 40 mg/d (severe AH)**	HR 0.78	Dose: 28 days, stop if Lille ≥0.45	**A**
42	Nguyen-Khac 2011 (NEJM)	**N-acetylcysteine + prednisolone (severe AH)**	HR 0.73	Dose: IV 1st 5 days	**B**
43	Cabré 2000; AASLD guideline	**Nutritional support 35–40 kcal/kg, 1.2–1.5 g/kg protein**	HR 0.75	Dose: Enteral preferred	**A**
44	Standard of care	**Thiamine repletion ≥500 mg/d IV ×3d**	HR 0.85	Dose: Prevent Wernicke	**A**
45	Mohammad 2012	**Zinc supplementation 50 mg/d**	HR 0.88	Dose: Elemental zinc	**C**
46	Lancet 2018 (Lee); 6-mo survival 84% vs 7%	**Early liver transplant (selected severe AH)**	HR 0.27	Dose: Mathurin 2011 criteria	**A**
47	Klatsky 2006	**Coffee ≥3 cups/d**	HR 0.74	Dose: ≥3 cups	**B**
48	Synergistic injury	**Smoking cessation**	HR 0.85	Dose: Sustained	**B**
49	ACIP; AASLD	**Vaccination (HAV, HBV, pneumococcal, influenza)**	HR 0.85	Dose: Age-appropriate	**A**
50	Pose 2020 (LIVERHOPE-SAFETY)	**Statin in compensated cirrhosis**	HR 0.59	Dose: Simvastatin 20–40 mg	**B**
51	Bass 2010 (NEJM)	**Rifaximin 550 mg BID (HE history)**	HR 0.58	Dose: Daily	**A**
52	Sort 1999; ANSWER 2018	**Albumin (SBP, HRS, large-volume paracentesis)**	HR 0.65	Dose: 1.5 g/kg d1, 1 g/kg d3	**A**
53	PREDESCI 2019	**NSBB if CSPH (carvedilol)**	HR 0.51	Dose: 6.25–12.5 mg/d	**A**
54	Singal 2014	**HCC surveillance q6mo (cirrhosis)**	HR 0.63	Dose: US + AFP	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
55	Marcellin 2013; Hsu 2020 meta (lower HCC vs ETV)	**Tenofovir disoproxil 300 mg/d**	HR 0.32	Dose: 300 mg/d	A
56	Agarwal 2018; renal-safer	**Tenofovir alafenamide 25 mg/d**	HR 0.35	Dose: 25 mg/d	A
57	Hosaka 2013; Wong 2013	**Entecavir 0.5 mg/d (naïve)**	HR 0.37	Dose: 0.5 mg/d empty stomach	A
58	Lampertico 2009; HBsAg loss 5–10%	**Pegylated IFN-α 180 µg/wk × 48 wk**	HR 0.55	Dose: 48 wk course	B
59	Beasley 1983; vertical transmission prevention	**HBIG + vaccine (perinatal prophylaxis)**	HR 0.10	Dose: <12 h postpartum	A
60	Pan 2016 (NEJM)	**Maternal TDF (3rd trimester, HBV DNA >2×105)**	HR 0.05	Dose: Wk 28–delivery	A
61	Singal 2014; Zhang 2004 RCT	**HCC surveillance q6mo US ± AFP**	HR 0.63	Dose: Q6 mo	A
62	Inoue 2009 (JPHC)	**Coffee ≥3 cups/d**	HR 0.74	Dose: ≥3 cups	B
63	Donato 2002	**Alcohol abstinence**	HR 0.60	Dose: 0 g/d (synergistic HCC)	A
64	Lee 2009 meta	**Smoking cessation**	HR 0.75	Dose: Sustained	B
65	Hsiang 2015; Tsan 2012 (HBV-specific)	**Statin therapy**	HR 0.62	Dose: Any statin ≥1 yr	B
66	Simon 2018 (NEJM); HCC reduction; weigh GI bleed	**Low-dose aspirin (81 mg/d)**	HR 0.71	Dose: 81 mg/d	B
67	Lai 2012 (HBV cohort)	**Metformin (if diabetic)**	HR 0.50	Dose: ≥1500 mg/d	B
68	Liu & Wu 2010; QALY gain in endemic regions	**Aflatoxin avoidance (food storage)**	HR 0.80	Dose: Population-level	B
69	Farnik 2013; modest signal	**Vitamin D repletion (≥30 ng/mL)**	HR 0.88	Dose: 1000–4000 IU/d	C
70	ACIP; prevents superinfection mortality	**HAV vaccination (susceptible)**	HR 0.85	Dose: 2 doses	A
71	ASTRAL-1/2/3; SVR12 ≈ 98%	**Sofosbuvir/Velpatasvir 12 wk (pangenotypic)**	HR 0.26	Dose: 400/100 mg × 12 wk	A
72	ENDURANCE; EXPEDITION	**Glecaprevir/Pibrentasvir 8 wk (non-cirrh)**	HR 0.27	Dose: 300/120 mg × 8 wk	A

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
73	Backus 2019; van der Meer 2012 (IFN era); ANRS CO22 HEPATHER	**Any DAA achieving SVR12 (genotype-tailored)**	HR 0.29	Dose: Per AASLD/IDSA	**A**
74	Singal 2014; lifelong if cirrhosis	**HCC surveillance post-SVR (if F3-F4)**	HR 0.63	Dose: Q6 mo US ± AFP	**A**
75	Hutchinson 2005; synergistic	**Alcohol abstinence**	HR 0.40	Dose: 0 g/d	**A**
76	Freedman 2009 (HALT-C)	**Coffee ≥3 cups/d**	HR 0.74	Dose: ≥3 cups	**B**
77	Pessione 2001	**Smoking cessation**	HR 0.78	Dose: Sustained	**B**
78	Mohanty 2016; Simon 2019	**Statin therapy**	HR 0.55	Dose: Atorva/simva	**B**
79	Simon 2018 (NEJM)	**Low-dose aspirin 81 mg/d**	HR 0.65	Dose: 81 mg/d	**B**
80	Donadon 2010	**Metformin (if diabetic)**	HR 0.62	Dose: ≥1500 mg/d	**B**
81	Iron accelerates fibrosis	**Avoid iron supplementation if not deficient**	HR 0.92	Dose: —	**C**
82	Superinfection prevention	**HAV + HBV vaccination**	HR 0.88	Dose: Per ACIP	**A**
83	PREDESCI 2019	**NSBB if CSPH (compensated cirrhosis)**	HR 0.51	Dose: Carvedilol 6.25–12.5 mg	**A**
84	EASL & AASLD guidelines; 80% remission	**Prednisone 40–60 mg/d taper (induction)**	HR 0.40	Dose: Taper to 5–10 mg/d	**A**
85	Combination induction + maintenance	**Azathioprine 1–2 mg/kg/d (maintenance)**	HR 0.45	Dose: TPMT-guided	**A**
86	Manns 2010 (Gastroenterology); fewer steroid AEs	**Budesonide 9 mg/d (non-cirrhotic)**	HR 0.55	Dose: Taper	**B**
87	Zachou 2011 retrospective; AZA-intolerant	**Mycophenolate mofetil 1–2 g/d (2nd line)**	HR 0.60	Dose: BID	**B**
88	Aqel 2004; van Thiel 1995	**Tacrolimus (refractory)**	HR 0.70	Dose: Trough 3–6 ng/mL	**C**
89	Standard prevention	**Vit D + Ca + bisphosphonate (steroid bone)**	HR 0.80	Dose: Per FRAX	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
90	5-yr survival ~80%	**Liver transplantation (decompensated)**	HR 0.30	Dose: Per MELD	**A**
91	Singal 2014	**HCC surveillance q6mo (cirrhosis)**	HR 0.63	Dose: US + AFP	**A**
92	Synergistic injury	**Alcohol abstinence**	HR 0.75	Dose: 0 g/d	**B**
93	General hepatoprotection	**Coffee ≥3 cups/d**	HR 0.80	Dose: ≥3 cups	**C**
94	ACIP; AASLD	**Vaccinations (HAV, HBV, pneumo, flu, COVID, zoster age-app.)**	HR 0.85	Dose: Pre-immunosuppression ideal	**A**
95	Poupon 1991; Corpechot 2008; Harms 2019 transplant-free survival	**UDCA 13–15 mg/kg/d (1st-line)**	HR 0.46	Dose: 13–15 mg/kg/d	**A**
96	POISE 2016 (NEJM); FDA 2016 (boxed warning advanced)	**Obeticholic acid 5–10 mg (UDCA non-responder)**	HR 0.60	Dose: 5–10 mg/d	**A**
97	BEZURSO 2018 (NEJM); Corpechot	**Fenofibrate or bezafibrate (add-on)**	HR 0.39	Dose: Bezafibrate 400 mg/d	**A**
98	ELATIVE 2024 (NEJM); FDA approved Jun 2024	**Elafibranor 80 mg/d (PPARα/δ; 2024)**	HR 0.55	Dose: 80 mg/d	**A**
99	RESPONSE 2024; FDA approved Aug 2024	**Seladelpar 10 mg/d (PPARδ; 2024)**	HR 0.60	Dose: 10 mg/d	**A**
100	1st-line pruritus	**Cholestyramine 4 g 1–4×/d (pruritus)**	HR 0.95	Dose: Sequester away from UDCA by ≥4 h	**B**
101	Tandon 2007 meta	**Rifampin 150–300 mg BID (refractory pruritus)**	HR 0.92	Dose: Monitor LFTs	**B**
102	Cholestatic deficiency	**Fat-soluble vitamin (A,D,E,K) repletion**	HR 0.85	Dose: Cholestyramine-aware dosing	**B**
103	Standard of care	**Ca + vit D + bisphosphonate (osteoporosis prev)**	HR 0.80	Dose: Per FRAX/DXA	**A**
104	Trivedi 2016	**HCC surveillance q6mo (cirrhosis or men)**	HR 0.63	Dose: US + AFP	**A**
105	5-yr survival ~85%	**Liver transplantation (advanced/refractory)**	HR 0.28	Dose: MELD or pruritus indication	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
106	General hepatoprotection	**Alcohol moderation /abstinence**	HR 0.85	Dose: Minimize	C
107	Limited PBC data	**Coffee ≥3 cups/d**	HR 0.85	Dose: ≥3 cups	C
108	Lindor 1997; benefit uncertain	**UDCA 13–15 mg/kg/d (debated)**	HR 0.85	Dose: 13–15 mg/kg/d	C
109	Davies 2008; Tabibian 2017 RCT	**Oral vancomycin 50 mg/kg/d (peds; investigational)**	HR 0.70	Dose: Investigational	C
110	Aabakken 2017 ESGE	**Endoscopic dilation of dominant strictures**	HR 0.65	Dose: ERCP-guided	A
111	Reduces colectomy, CRC, possibly PSC progression	**IBD treatment optimization**	HR 0.85	Dose: 5-ASA / biologics	A
112	Rizvi 2018; earlier detection	**Annual MRCP + CA 19-9 (CCA surveillance)**	HR 0.70	Dose: Annual	A
113	Soetikno 2002; pan-colitis	**Annual colonoscopy if IBD (CRC surveillance)**	HR 0.50	Dose: Annual	A
114	5-yr survival ~85%; recurrence ~20%	**Liver transplantation (advanced)**	HR 0.30	Dose: MELD or CCA/refractory cholangitis	A
115	Lemoinne 2018 pilot	**Fenofibrate (investigational)**	HR 0.70	Dose: 160 mg/d	C
116	Deficiency common	**Fat-soluble vitamin repletion (A,D,E,K)**	HR 0.85	Dose: Cholestatic dosing	B
117	Reduce 2-hit injury	**Alcohol abstinence**	HR 0.80	Dose: 0 g/d	B
118	Reduces CCA risk	**Smoking cessation**	HR 0.78	Dose: Sustained	B
119	Singal 2014	**HCC surveillance q6mo (cirrhosis)**	HR 0.63	Dose: US + AFP	A
120	Niederau 1996; pre-cirrhotic essentially normalizes life expectancy	**Therapeutic phlebotomy (weekly→maintenance, target ferritin 50–100)**	HR 0.20	Dose: 500 mL weekly until target, then q2–4 mo	A
121	Rombout-Sestrienkova 2017	**Erythrocytapheresis (alternative)**	HR 0.22	Dose: Q4–8 wk maintenance	A

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
122	Phatak 2010 (deferasirox PoC)	**Deferasirox / deferiprone (if anemic, phleb-intolerant)**	HR 0.40	Dose: Oral chelator	**B**
123	Reduces absorption	**Avoid iron supplements & vitamin C with iron-rich meals**	HR 0.80	Dose: Dietary counseling	**B**
124	Modest	**Reduce heme iron (red meat moderation)**	HR 0.88	Dose: <3 servings/wk	**C**
125	FDA advisory; sepsis prevention	**Avoid raw shellfish (Vibrio vulnificus risk)**	HR 0.92	Dose: Cooked only	**A**
126	Fletcher 2002; >60 g/d 9× cirrhosis risk	**Alcohol abstinence (synergistic with iron)**	HR 0.30	Dose: 0 g/d	**A**
127	Bardou-Jacquet 2017	**HCC surveillance q6mo (cirrhosis)**	HR 0.63	Dose: US + AFP	**A**
128	Detects pre-symptomatic	**First-degree relative HFE genotyping**	HR 0.75	Dose: Cascade testing	**A**
129	Chelates iron; reduces fibrosis	**Coffee ≥3 cups/d**	HR 0.78	Dose: ≥3 cups	**B**
130	Walshe 1956; long-term cohort	**D-Penicillamine 750–1500 mg/d (induction)**	HR 0.30	Dose: Divided BID-QID + pyridoxine	**A**
131	Walshe 1982; preferred if penicillamine-intolerant	**Trientine 750–1500 mg/d (better tolerated)**	HR 0.30	Dose: Divided BID-QID	**A**
132	Brewer 1998; presymptomatic & maintenance	**Zinc acetate 50 mg TID (maintenance)**	HR 0.40	Dose: 150 mg/d	**A**
133	Adjunctive	**Low-copper diet (avoid liver, shellfish, nuts, chocolate, mushrooms)**	HR 0.85	Dose: Year 1 strict	**B**
134	5-yr survival ~85%; cures hepatic disease	**Liver transplant (ALF or refractory cirrh.)**	HR 0.25	Dose: Urgent if ALF	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
135	Identifies presymptomatic	**First-degree relative ATP7B sequencing**	HR 0.70	Dose: Cascade testing	A
136	Lung-dominant; hepatic comorbidity	**Smoking cessation**	HR 0.40	Dose: Sustained	A
137	Synergistic hepatic injury	**Alcohol abstinence**	HR 0.55	Dose: 0 g/d	A
138	5-yr survival ~80%; recipient becomes PiMM	**Liver transplantation (cures hepatic α1ATD)**	HR 0.25	Dose: MELD or HCC	A
139	AROAAT-2002; reduces hepatic Z-protein 90%; Phase 3 ongoing	**Fazirsiran siRNA (investigational)**	HR 0.50	Dose: SC q12wk	C
140	Standard	**HAV + HBV + pneumococcal + influenza vacc.**	HR 0.85	Dose: ACIP	A
141	Standard if cirrhosis	**HCC surveillance q6mo (cirrhosis)**	HR 0.63	Dose: US + AFP	A
142	Standard	**Vitamin K if cholestatic**	HR 0.85	Dose: Repletion	B
143	General hepatoprotection	**Coffee ≥3 cups/d**	HR 0.80	Dose: ≥3 cups	C
144	Modifies lifestyle counseling	**Family screening (SERPINA1 genotyping)**	HR 0.75	Dose: First-degree	A
145	Cornerstone — reduces fibrogenesis	**Etiology-specific therapy (DAA / NA / abstinence / UDCA / immunosup)**	HR 0.40	Dose: Disease-tailored	A
146	PREDESCI 2019 (Lancet) — prevents decompensation	**NSBB (carvedilol 6.25–12.5 mg/d) if CSPH**	HR 0.51	Dose: Carvedilol preferred	A
147	Garcia-Tsao 2017 AASLD	**Endoscopic variceal ligation (large varices)**	HR 0.60	Dose: Until eradication	A
148	Singal 2014 meta	**HCC surveillance q6mo US ± AFP**	HR 0.63	Dose: Q6 mo	A
149	AASLD	**Vaccines: HAV, HBV, pneumo, flu, COVID, zoster**	HR 0.85	Dose: Per ACIP	A
150	Renal & GI safety	**Avoid NSAIDs, nephrotoxins, hepatotoxins**	HR 0.80	Dose: Counseling	A

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
151	Kim 2017; Pose 2020 safety	**Statin (simvastatin 20–40 mg)**	HR 0.59	Dose: 20–40 mg/d	**B**
152	Kennedy 2017 meta	**Coffee ≥3 cups/d**	HR 0.74	Dose: ≥3 cups	**B**
153	Major modifiable	**Alcohol abstinence**	HR 0.50	Dose: 0 g/d	**A**
154	Reduces HCC	**Smoking cessation**	HR 0.78	Dose: Sustained	**B**
155	Simon 2018 (NEJM)	**Low-dose aspirin (HCC reduction)**	HR 0.71	Dose: 81 mg/d; weigh GI bleed risk	**B**
156	Plank 2008; Tsien 2012	**Late-evening protein snack + BCAA**	HR 0.85	Dose: BCAA 12 g/d	**B**
157	Standard	**Sodium <2 g/d (ascites prevention)**	HR 0.85	Dose: <2 g/d	**B**
158	Survival benefit threshold	**Liver transplant evaluation (MELD ≥15)**	HR 0.40	Dose: Refer early	**A**
159	OPTN; 1-yr survival ~90%	**Liver transplantation (when feasible)**	HR 0.30	Dose: Per MELD / acute listing	**A**
160	Salerno 2007 meta; pre-emptive TIPS (PCH) HR 0.39	**TIPS (refractory ascites or variceal rebleed)**	HR 0.50	Dose: PSG <12 mmHg target	**A**
161	Bass 2010 (NEJM)	**Rifaximin 550 mg BID (HE prevention)**	HR 0.58	Dose: Daily	**A**
162	Sharma 2009; secondary prophylaxis	**Lactulose titrated to 2–3 BMs/d**	HR 0.65	Dose: Per response	**A**
163	Sort 1999; Caraceni 2018 ANSWER	**Albumin (SBP, HRS, LVP >5 L)**	HR 0.62	Dose: 1.5 g/kg d1, 1 g/kg d3; ANSWER long-term in selected	**A**
164	Wong 2021 CONFIRM (FDA 2022)	**Terlipressin + albumin (HRS-AKI)**	HR 0.65	Dose: Per protocol	**A**
165	Esrailian 2007	**Midodrine + octreotide (HRS, terlipressin unavailable)**	HR 0.85	Dose: Standard	**B**
166	Gines 1990	**SBP prophylaxis (norfloxacin/cipro 400 mg/d)**	HR 0.50	Dose: Daily	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
167	Garcia-Tsao 2017	**Urgent endoscopy + band ligation (variceal bleed)**	HR 0.55	Dose: Within 12 h	**A**
168	Baveno VII	**Vasoactive (octreotide/terlipressin) × 3–5 d (var bleed)**	HR 0.70	Dose: IV continuous	**A**
169	Fernandez 2006	**Prophylactic ceftriaxone × 7 d (var bleed)**	HR 0.60	Dose: 1 g/d	**A**
170	Garcia-Tsao 2017	**NSBB titration (post-bleed secondary prophylaxis)**	HR 0.55	Dose: Carvedilol/propranolol	**A**
171	AASLD	**Spironolactone ± furosemide (ascites)**	HR 0.75	Dose: Step-up	**A**
172	AASLD	**Sodium restriction <2 g/d**	HR 0.80	Dose: Strict	**A**
173	AASLD HE guideline	**Trigger avoidance (NSAIDs, sedatives, infection screening)**	HR 0.75	Dose: Vigilance	**A**
174	Continued even if decompensated	**Etiology-specific therapy (antivirals/abstinence/UDCA/immunosup)**	HR 0.55	Dose: Disease-tailored	**A**
175	Singal 2014	**HCC surveillance q6mo (if MELD <20 and LT candidate)**	HR 0.63	Dose: US + AFP	**A**
176	Roayaie 2013; 5-yr survival 60–70%	**Surgical resection (BCLC 0/A, preserved fx)**	HR 0.20	Dose: Anatomic preferred	**A**
177	Mazzaferro 1996; 5-yr 70%	**Liver transplant (Milan / UCSF criteria)**	HR 0.15	Dose: Per allocation	**A**
178	Cucchetti 2013; comparable to resection for ≤2 cm	**Ablation (RFA / MWA) ≤3 cm**	HR 0.25	Dose: Per nodule	**A**
179	Llovet 2002 RCT; BCLC B	**TACE (transarterial chemoembolization)**	HR 0.55	Dose: Per nodule	**A**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
180	Salem 2016; LEGACY	**TARE / Y-90 radioembolization**	HR 0.55	Dose: Per dosimetry	**A**
181	IMbrave150 2020 (NEJM); mOS 19.2 mo	**Atezolizumab + Bevacizumab (1L advanced)**	HR 0.58	Dose: Q3wk	**A**
182	HIMALAYA 2022 (NEJM Evid)	**Durvalumab + Tremelimumab (STRIDE; 1L advanced)**	HR 0.78	Dose: Single trem prime	**A**
183	RATIONALE-301 2023	**Tislelizumab (1L; non-inferior to sorafenib)**	HR 0.85	Dose: 200 mg q3wk	**A**
184	REFLECT 2018 (Lancet); non-inferior sorafenib	**Lenvatinib (1L if IO contraindicated)**	HR 0.92	Dose: Weight-based	**B**
185	SHARP 2008 (NEJM)	**Sorafenib (1L if IO/lenv contraindicated)**	HR 0.69	Dose: 400 mg BID	**B**
186	CELESTIAL 2018	**Cabozantinib (2L post-sorafenib)**	HR 0.76	Dose: 60 mg/d	**A**
187	REACH-2 2019	**Ramucirumab (AFP ≥400, 2L)**	HR 0.71	Dose: 8 mg/kg q2wk	**A**
188	RESORCE 2017	**Regorafenib (2L post-sorafenib)**	HR 0.63	Dose: 160 mg cycle	**A**
189	KEYNOTE-394 2022	**Pembrolizumab (Asia; KEYNOTE-394)**	HR 0.79	Dose: 200 mg q3wk	**B**
190	CheckMate-9DW 2024 1L positive	**Nivolumab + Ipilimumab (2L; or 1L emerging)**	HR 0.79	Dose: Per CheckMate-040/9DW	**A**
191	Reduces recurrence post-curative	**Continue/initiate underlying etiology therapy**	HR 0.65	Dose: Per disease	**A**
192	Symptom-directed	**Best supportive care (BCLC D)**	HR 1.00	Dose: Palliative	**A**
193	Lee 2009 non-APAP (Gastro); APAP standard	**N-acetylcysteine IV (APAP & non-APAP)**	HR 0.40	Dose: 150-50-100 mg/kg protocol	**A**
194	Case series; Amanita silibinin RCT-supported	**Specific antidote (e.g., L-carnitine for VPA, silibinin for Amanita)**	HR 0.55	Dose: Toxin-specific	**B**

#	Reference(s) / cited source	Intervention	Effect size (95% CI)	Endpoint / dose	Rate
195	AASLD ALF 2023	**Antivirals (entecavir/tenofovir HBV; acyclovir HSV)**	HR 0.60	Dose: Per pathogen	A
196	Larsen 2016 (J Hepatol)	**High-volume plasma exchange (HVPE)**	HR 0.59	Dose: 8–12 L over 3 sessions	A
197	Cardoso 2018; ammonia clearance	**CRRT for AKI / hyperammonemia (>150 µmol/L)**	HR 0.70	Dose: Continuous	A
198	Murphy 2004; cerebral edema	**ICP management: hypertonic saline / mannitol**	HR 0.75	Dose: Per ICP	A
199	Karvellas 2010; controversial	**Targeted temperature management (33–35°C)**	HR 0.92	Dose: Selected ICP refractory	C
200	Bernal 2013; 1-yr ~80%	**Emergency liver transplant (urgent listing)**	HR 0.30	Dose: King's College / Clichy criteria	A
201	AASLD ALF	**Mechanical ventilation, vasopressors as needed**	HR 0.85	Dose: ICU standard	A
202	Standard obstetric mgmt	**Expedited delivery (HELLP/AFLP)**	HR 0.30	Dose: Definitive	A
203	Tortora 2019	**Plasma exchange ± chelation (Wilsonian ALF)**	HR 0.50	Dose: Bridge to LT	B

2.5–2.9 · Internet-verified landmark references (Installments 1–5)

This section upgrades bibliography-only analyses (Section 3) into rated reference rows. For each landmark trial named in those analyses, the primary endpoint and effect size were located on the internet from the trial's primary publication (or an equivalent peer-reviewed / registry source) and are cited in the source column. Five installments are complete, covering 22 analyses. Most rows are pivotal randomised controlled trials or meta-analyses of randomised trials (Class A); a minority rest on observational cohorts where randomisation is impossible or unethical (fitness, transplant, opioid-agonist therapy, influenza vaccination) and are rated Class C accordingly. The rating column shows each row's class. These are installments — they cover the flagship evidence, not every intervention; the rare-disease installment in particular shows five high-mortality exemplars from the Pareto frontier rather than the full orphan-disease list.

2.5 · Installment 1 — cardiometabolic cluster (13 references — A:13)

Analyses: Cardiovascular, Heart Disease, Cholesterol and Metabolic Disease.

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
PARADIGM-HF (McMurray et al., NEJM 2014) AHA Circ Heart Failure 2016 / NCT01035255	Cardiovascular / Heart Disease	HFrEF (EF <=40%)	**Sacubitril/valsartan vs enalapril:** HR 0.80 (0.73-0.87); CV death HR 0.80 (0.71-0.89); all-cause death HR 0.84 (0.76-0.93)	CV death or HF hospitalisation	A
DAPA-HF (McMurray et al., NEJM 2019) NEJM 2019;381:1995 (NCT03036124)	Cardiovascular / Heart Disease	HFrEF (EF <=40%)	**Dapagliflozin vs placebo:** Primary HR 0.74 (0.65-0.85); CV death HR 0.82 (0.69-0.98); all-cause death HR 0.83 (0.71-0.97)	Worsening HF or CV death	A
EMPEROR-Reduced (Packer et al., NEJM 2020) NEJM 2020;383:1413	Cardiovascular / Heart Disease	HFrEF (EF <=40%)	**Empagliflozin vs placebo:** Primary HR ~0.75 (0.65-0.86); composite 19.4% vs 24.7%	CV death or HF hospitalisation	A
FOURIER (Sabatine et al., NEJM 2017) NEJM 2017;376:1713 (NCT01764633)	Cholesterol / Cardiovascular	Stable ASCVD on statin, LDL >=70 mg/dL	**Evolocumab (PCSK9i) vs placebo:** MACE HR 0.85 (0.79-0.92); ~15% RRR	CV death, MI, stroke, unstable-angina hosp., or revascularisation	A
ODYSSEY OUTCOMES (Schwartz et al., NEJM 2018) NEJM 2018;379:2097	Cholesterol / Cardiovascular	Recent acute coronary syndrome on high-intensity statin	**Alirocumab (PCSK9i) vs placebo:** MACE HR 0.85 (0.78-0.93); ~15% reduction	Composite MACE (CHD death, MI, ischaemic stroke, unstable-angina hosp.)	A
SPRINT (NEJM 2015; final report NEJM 2021) NEJM 2015;373:2103; final NEJM 2021	Cardiovascular / Heart Disease	High-CV-risk hypertension, non-diabetic	**Intensive SBP target <120 vs <140 mmHg:** Primary HR 0.75 (0.64-0.89); all-cause mortality HR 0.73 (0.60-0.90)	MI, ACS, stroke, acute HF, or CV death	A
RE-LY (Connolly et al., NEJM 2009) BMJ Open analysis PMC3533028 / NEJM 2009	Cardiovascular (atrial fibrillation)	Atrial fibrillation	**Dabigatran 150 mg vs warfarin:** Stroke/systemic embolism RR 0.65 (0.52-0.81), superiority	Stroke or systemic embolism	A
ARISTOTLE (Granger et al., NEJM 2011) NEJM 2011;365:981; review PMC3471365	Cardiovascular (atrial fibrillation)	Atrial fibrillation	**Apixaban vs warfarin:** Stroke/systemic embolism HR 0.79 (0.66-0.95), superior; less major bleeding	Stroke or systemic embolism	A
ROCKET-AF (Patel et al., NEJM 2011) Review PMC3444866 / NEJM 2011	Cardiovascular (atrial fibrillation)	Atrial fibrillation, higher stroke risk	**Rivaroxaban vs warfarin:** Stroke/systemic embolism non-inferior to warfarin; reduced intracranial haemorrhage	Stroke or systemic embolism	A

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
EMPA-REG OUTCOME (Zinman et al., NEJM 2015) Protocol/registry NCT03594110; NEJM 2015;373:2117	Metabolic / Cardiovascular	T2D with established CVD	**Empagliflozin vs placebo:** 3-point MACE HR 0.86 (0.74-0.99); CV death HR 0.62 (0.49-0.77); HF hosp HR 0.65 (0.50-0.85)	CV death, non-fatal MI, or non-fatal stroke	A
LEADER (Marso et al., NEJM 2016) NEJM 2016;375:311; CVOT review NCT03496298	Metabolic / Cardiovascular	T2D at high CV risk	**Liraglutide (GLP-1 RA) vs placebo:** 3-point MACE HR 0.87 (0.78-0.97); ~13% reduction	CV death, non-fatal MI, or non-fatal stroke	A
SUSTAIN-6 (Marso et al., NEJM 2016) NEJM 2016;375:1834; CVOT review	Metabolic / Cardiovascular	T2D at high CV risk	**Semaglutide (GLP-1 RA) vs placebo:** 3-point MACE HR 0.74 (0.58-0.95)	CV death, non-fatal MI, or non-fatal stroke	A
CANVAS Program (Neal et al., NEJM 2017) CVOT review NCT03496298; NEJM 2017;377:644	Metabolic / Cardiovascular	T2D with/at high risk of CVD	**Canagliflozin vs placebo:** 3-point MACE HR 0.86 (~14% reduction; p=0.02 superiority)	CV death, non-fatal MI, or non-fatal stroke	A

2.6 · Installment 2 — neuro / psychiatric cluster (9 references — A:9)

Analyses: Dementia, Depression, ADHD, ASD, Parkinson's Disease and Bipolar II.

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
Lancet Commission on Dementia 2024 (Livingston et al., Lancet 2024) Lancet 2024; thelancet.com commission	Dementia	Population (life-course)	**Addressing 14 modifiable risk factors:** ~45% of dementia cases potentially preventable (population attributable fraction)	Incident dementia (PAF, not a single RCT effect)	A
FINGER (Ngandu et al., Lancet 2015;385:2255) Lancet 2015;385:2255-2263	Dementia	At-risk older adults (general population)	**2-yr multidomain: diet + exercise + cognitive training + vascular monitoring vs control:** Improved / preserved cognition (neuropsychological test battery) vs control	Change in cognitive composite at 2 years	A
Cipriani et al. antidepressant NMA (Lancet 2018;391:1357) Lancet 2018;391:1357-1366	Depression	Adults, major depressive disorder	**21 antidepressants vs placebo (network meta-analysis, 522 RCTs):** All > placebo for response, OR range 1.37-2.13; rating-scale SMD 0.30 (0.26-0.34) - statistically robust, clinical magnitude debated	Response (>=50% symptom reduction) at ~8 weeks	A
Cortese et al. ADHD medication NMA (Lancet Psychiatry 2018;5:727) Lancet Psychiatry 2018;5:727-738	ADHD	Children, adolescents and adults with ADHD	**Stimulants and atomoxetine vs placebo (NMA, 133 double-blind RCTs):** Stimulants & atomoxetine superior to placebo; amphetamines most efficacious (clinician-rated SMD up to ~ -1.0 in children)	Change in ADHD core-symptom severity at ~12 weeks	A
RUPP risperidone trial (McCracken et al., NEJM 2002;347:314) NEJM 2002;347:314-321	ASD	Children with autism and serious behavioural problems	**Risperidone vs placebo:** Response 69% (34/49) vs ~12% placebo; effect size d ~1.2 (large)	Irritability (Aberrant Behaviour Checklist) at 8 weeks	A

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
Pharmacological/behavioural meta-analysis of ASD irritability (Iturmendi-Sabater et al., 2024) Mol Autism 2024 (PMID 38263251)	ASD	ASD with irritability/emotional dysregulation	**Risperidone; aripiprazole; parent training:** Risperidone Hedges' g -0.857 (high certainty); aripiprazole g -0.559 (high); parent training g -0.893 (moderate)	Irritability rating scales	**A**
DBS for Parkinson's RCT (Deuschl et al., NEJM 2006;355:896) NEJM 2006;355:896-908	Parkinson's	Advanced PD with motor complications	**Subthalamic deep-brain stimulation + medication vs medical management:** ~10-point improvement in PDQ-39 quality of life; significant motor improvement; meta-analytic STN motor effect size ~2.6	Quality of life (PDQ-39) and UPDRS-III motor score	**A**
Maintenance pharmacotherapy meta-analysis (Vazquez et al., Int J Neuropsychopharmacol 2011) Int J Neuropsychopharmacol 2011;14:1029	Bipolar II	Bipolar disorder, maintenance phase	**Mood stabilisers / antipsychotics (lithium, quetiapine, lamotrigine, etc.) vs placebo:** Any-mood-episode relapse RR 0.68 (0.60-0.77)	Relapse to any mood episode	**A**
EMBOLDEN I/II quetiapine trials (Young et al., J Clin Psychiatry 2010) J Clin Psychiatry 2010;71:150; combined analysis PMC4230312	Bipolar II	Bipolar I/II depression	**Quetiapine monotherapy vs placebo (lithium / paroxetine active comparators):** Quetiapine effective for acute bipolar (incl. bipolar II) depression vs placebo; note lithium did NOT separate from placebo in EMBOLDEN I	MADRS depressive-symptom change at 8 weeks	**A**

2.7 · Installment 3 — oncology cluster (8 references — A:8)

Analyses: Cancer, Brain (malignancy / stroke / Alzheimer's) and Lymphoma / Waldenstrom.

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
KEYNOTE-189 (Gandhi et al., NEJM 2018) NEJM 2018;378:2078; JCO 2023 5-yr (NCT02578680)	Cancer	Metastatic nonsquamous NSCLC, no EGFR/ALK alteration	**Pembrolizumab + pemetrexed-platinum vs chemo + placebo:** OS HR 0.49 (0.38-0.64) initial; 5-yr OS HR 0.60 (0.50-0.72); PFS HR 0.52 (0.43-0.64)	Overall survival and progression-free survival	**A**
EBCTCG adjuvant tamoxifen meta-analysis (Lancet 2011) EBCTCG, Lancet 2011;378:771 (15-yr overview)	Cancer	Oestrogen-receptor-positive early breast cancer	**~5 years adjuvant tamoxifen vs none:** ~13% absolute reduction in recurrence and ~9.1% absolute reduction in breast-cancer mortality (p<0.00001)	15-yr recurrence and breast-cancer mortality	**A**
Stupp protocol (Stupp et al., NEJM 2005;352:987) NEJM 2005;352:987-996; 5-yr Lancet Oncol 2009	Brain (glioblastoma)	Newly diagnosed glioblastoma	**Radiotherapy + concomitant/adjuvant temozolomide vs radiotherapy alone:** Death HR 0.63 (0.52-0.75); median OS 14.6 vs 12.1 mo; 2-yr OS 26.5% vs 10.4% (5-yr HR 0.6)	Overall survival	**A**
EF-14 tumour-treating fields (Stupp et al., JAMA 2017;318:2306) JAMA 2017;318:2306-2316	Brain (glioblastoma)	Newly diagnosed glioblastoma after chemoradiation	**Tumour-treating fields + maintenance temozolomide vs temozolomide alone:** ~37% reduction in risk of death; median OS extended ~5 months; 5-yr survival ~13%	Overall and progression-free survival	**A**

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
Late-window thrombectomy (DAWN, Nogueira et al., NEJM 2018; DEFUSE-3, Albers et al., NEJM 2018) NEJM 2018;378:11 (DAWN); NEJM 2018;378:708 (DEFUSE-3)	Brain (ischaemic stroke)	Large-vessel-occlusion stroke, 6-24 h from onset, clinical-imaging mismatch	**Endovascular thrombectomy + standard care vs standard care:** DAWN: 90-day functional independence (mRS 0-2) 49% vs 13%; DEFUSE-3 confirmatory (45% vs 17%)	90-day functional independence (modified Rankin 0-2)	A
CLARITY-AD lecanemab (van Dyck et al., NEJM 2023;388:9) NEJM 2023;388:9-21; CLARITY-AD	Brain (Alzheimer's)	Early symptomatic Alzheimer's disease (amyloid-positive)	**Lecanemab (anti-amyloid antibody) vs placebo:** Slowed clinical decline: CDR-SB difference -0.45 (~27% relative slowing) at 18 months; modest magnitude, ARIA safety signal	Change in CDR-Sum of Boxes at 18 months	A
iNNOVATE (Dimopoulos/Buske et al., NEJM 2018; final JCO 2022) NEJM 2018;378:2399; JCO 2022;40:52	Lymphoma / Waldenstrom	Waldenstrom macroglobulinemia	**Ibrutinib + rituximab vs placebo + rituximab:** PFS HR 0.250 (p<0.0001); median PFS not reached vs 20.3 months	Progression-free survival	A
ASPEN (Tam et al., Blood 2020;136:2038; final JCO 2023) Blood 2020;136:2038-2050; JCO 2023	Lymphoma / Waldenstrom	Symptomatic Waldenstrom macroglobulinemia (MYD88-mutant)	**Zanubrutinib vs ibrutinib (head-to-head):** CR/VGPR 28% vs 19% (p=0.09, NS); MRR ~77-78%; comparable efficacy with less atrial fibrillation (PFS HR 0.63, 0.36-1.12)	Complete or very-good partial response rate	A

2.8 · Installment 4 — remaining clinical analyses (10 references — A:6 · C:4)

Analyses: All-Cause Mortality, Osteoarthritis, BPH, Transplant, Pre-eclampsia, Immunology, Infectious-disease mortality, Self-caused mortality and Anxiety.

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
Cardiorespiratory fitness cohort (Mandsager et al., JAMA Netw Open 2018) JAMA Netw Open 2018;1(6):e183605 (observational)	All-Cause Mortality	122,007 adults undergoing treadmill testing	**Elite vs low cardiorespiratory fitness:** Adjusted all-cause mortality HR ~0.20 (elite vs low; 95% CI ~0.16-0.24); inverse, no ceiling	All-cause mortality (median 8.4 y)	C
ASPREE (McNeil et al., NEJM 2018) NEJM 2018;379:1519 (and 1499, 1509)	All-Cause Mortality	Healthy community-dwelling elderly (>=70 y)	**Low-dose aspirin 100 mg vs placebo (primary prevention):** All-cause mortality HR 1.14 (1.01-1.29) - HIGHER on aspirin; cancer death HR 1.31; no disability-free-survival benefit	All-cause mortality / disability-free survival	A
NSAID network meta-analysis (da Costa/Pereira et al., BMJ 2021) BMJ 2021;375:n2321	Osteoarthritis	Knee and hip osteoarthritis	**NSAIDs vs placebo (NMA of large RCTs):** Diclofenac 150 mg/day SMD -0.57 (-0.69 to -0.45); etoricoxib 60 mg/day SMD -0.58 (-0.74 to -0.43) - both exceed MCID	Osteoarthritis pain	A
MTOPS (McConnell et al., NEJM 2003) NEJM 2003;349:2387-2398	Benign Prostatic Hyperplasia	Men with moderate-severe symptomatic BPH	**Doxazosin + finasteride combination vs monotherapy / placebo:** Clinical-progression risk reduction vs placebo: combination 66%, doxazosin 39%, finasteride 34% (all p<=0.002)	Overall BPH clinical progression	A

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
Kidney transplant vs dialysis (Wolfe et al., NEJM 1999) NEJM 1999;341:1725-1730 (registry; randomisation not possible)	Universal Transplant Mortality	Waitlisted ESRD patients (USRDS registry)	**First cadaveric kidney transplant vs remaining on dialysis:** Long-term mortality reduction averaging ~66% (RR of death ~0.32); survival benefit from ~244 days post-transplant	Long-term all-cause mortality	C
ASPRE (Rolnik et al., NEJM 2017) NEJM 2017;377:613-622	Pre-eclampsia	High-risk singleton pregnancies (first-trimester algorithm)	**Aspirin 150 mg/day from 11-14 to 36 weeks vs placebo:** Preterm pre-eclampsia OR 0.38 (0.20-0.74); ~62% reduction; no effect on term PE	Preterm pre-eclampsia (<37 weeks)	A
PALISADE (PALISADE Group, NEJM 2018) NEJM 2018;379:1991-2001	Immunology (food allergy)	Peanut-allergic children/adolescents (4-17 y)	**AR101 peanut oral immunotherapy vs placebo:** Tolerated >=600 mg peanut protein at exit challenge: 67.2% vs 4.0% (difference 63.2 pts, 53.0-73.3; p<0.001)	Desensitisation at exit food challenge	A
Opioid agonist therapy (Sordo et al., BMJ 2017; Larochelle et al., Ann Intern Med 2018) BMJ 2017;357:j1550; Ann Intern Med 2018;169:137 (cohort; RCT unethical)	Self-Caused Mortality (overdose)	Opioid use disorder; after nonfatal overdose	**Methadone or buprenorphine (medication for OUD):** After nonfatal overdose, opioid-related mortality reduced ~59% (methadone) and ~38% (buprenorphine); ~50% all-cause reduction on treatment	All-cause and overdose mortality	C
Influenza vaccination in older adults (cohort meta-analyses) e.g. propensity-matched cohort PMC7564344 (observational, confounded)	US Mortality (infectious)	Community-dwelling adults >=65 y	**Seasonal influenza vaccination vs none:** All-cause mortality associated OR ~0.84 (0.75-0.93) propensity-matched; larger estimates likely inflated by healthy-vaccinee bias	All-cause mortality (influenza season)	C
CBT for anxiety disorders (Carpenter et al. 2018; Hofmann & Smits 2008) Depress Anxiety 2018; Carpenter meta-analysis	Anxiety	Adults with anxiety-related disorders	**Cognitive behavioural therapy vs placebo/control:** Placebo-controlled effect Hedges' g ~0.56 (Carpenter 2018); shrinks to g ~0.24 in most rigorous recent RCTs	Anxiety symptom severity change	A

2.9 · Installment 5 — rare disease (high-mortality exemplars) (5 references — A:5)

Analyses: Rare Disease Pareto targeting, shown via five high-impact orphan diseases with pivotal disease-modifying trials.

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
ENDEAR (Finkel et al., NEJM 2017) NEJM 2017;377:1723-1732	Rare Disease (spinal muscular atrophy)	Infants with symptomatic SMA type 1 (<=7 months)	**Nusinersen (intrathecal antisense oligonucleotide) vs sham:** Motor-milestone response 51% vs 0% sham (p<0.0001); significantly lower risk of death or permanent ventilation	Motor-milestone response; event-free (death/permanent ventilation) survival	A
VX17-445-102 (Middleton et al., NEJM 2019) NEJM 2019;381:1809-1819	Rare Disease (cystic fibrosis)	CF patients >=12 y, Phe508del-minimal-function genotype	**Elexacaftor-tezacaftor-ivacaftor (Trikafta) vs placebo:** ppFEV1 +14.3 points through 24 weeks; pulmonary exacerbations 63% lower; sweat chloride -41.8 mmol/L (all p<0.001)	Percent-predicted FEV1 (and exacerbation rate)	A

Reference (trial · source)	Oracle(s)	Population	Effect size (95% CI)	Endpoint	Rate
ATTR-ACT (Maurer et al., NEJM 2018) NEJM 2018;379:1007-1016	Rare Disease (transthyretin amyloid cardiomyopathy)	Wild-type or hereditary ATTR cardiomyopathy	**Tafamidis (transthyretin stabiliser) vs placebo, 30 months:** All-cause mortality 29.5% vs 42.9%, HR 0.70 (0.51-0.96); ~13.4% absolute mortality reduction; fewer CV hospitalisations (RRR 0.68); slower 6MWT/KCCQ decline	All-cause mortality + cardiovascular hospitalisation (hierarchical)	**A**
TRIUMPH (Hillmen et al., NEJM 2006) NEJM 2006;355:1233-1243	Rare Disease (paroxysmal nocturnal hemoglobinuria)	Transfusion-dependent PNH	**Eculizumab (anti-C5 complement inhibitor) vs placebo:** Haemoglobin stabilisation without transfusion 49% (21/43) vs 0% (0/44) placebo (p<0.001); ~87% reduction in intravascular haemolysis (LDH); ~50% transfusion-independent	Haemoglobin stabilisation; transfusion requirement	**A**
MSH (Charache et al., NEJM 1995) NEJM 1995;332:1317-1322; JAMA 2003;289:1645	Rare Disease (sickle cell anemia)	Adults with sickle cell anemia, >=3 crises/year	**Hydroxyurea vs placebo:** Annual painful crises reduced ~44% (median 2.5 vs 4.5/year); fewer hospitalisations, acute chest syndrome and transfusions; later 9-yr follow-up showed mortality benefit (Steinberg, JAMA 2003)	Annual rate of painful crises	**A**

Notes across installments: ROCKET-AF met a non-inferiority (not superiority) endpoint; the type-2-diabetes CVOTs (EMPA-REG, LEADER, SUSTAIN-6, CANVAS) report 3-point MACE; the Cipriani antidepressant SMD of 0.30 is statistically robust but its clinical magnitude is debated; the Lancet Commission 45% figure is a population attributable fraction, not a single-trial effect; lecanemab's CDR-SB benefit is a slowing of decline with an ARIA safety signal. In Installment 4: ASPREE is a deliberately included *null/harm* result (aspirin raised mortality in healthy elderly); the fitness, kidney-transplant, opioid-agonist-therapy and influenza-vaccine rows are observational (Class C) because randomisation is impossible or unethical, and the influenza all-cause-mortality association is materially inflated by healthy-vaccinee bias; the CBT-for-anxiety effect shrinks from g~0.56 to g~0.24 under the most rigorous placebo controls. Effect sizes are reproduced from the cited sources.

3 · Coverage, Limitations & Bibliography-Only Analyses

The Master Reference Table (Section 2) covers the four analyses whose dashboards bind a citation to a specific effect size and grade. The other 28 analyses store effect sizes but name their supporting literature only as trial-acronym lists (the dashboard's *evidence base* field), with no machine-readable link between an individual reference and an individual effect or endpoint. Rather than invent those pairings, their landmark trials are being looked up on the internet and promoted into rated rows in installments. **Five installments are now complete** (Section 2.5–2.9), covering **22 of the 28 analyses** with ~46 web-verified landmark references: the cardiometabolic cluster, the neuro/psychiatric cluster, the oncology cluster, a fourth installment of remaining clinical analyses, and a fifth covering rare disease (via five high-mortality orphan-disease exemplars with pivotal disease-modifying trials). Of the 6 not promoted, **four are non-interventional** (the Fiscal Impact Model, Life-Expectancy Shift Calculator, Atlas Coverage Count and MIMIC-III harness cite data tables, an economic model, mortality registries or a validation dataset — there is no treatment effect to rate) and **two are evidence-pending** (Portal Vein Thrombosis and McCune-Albright Syndrome rest on observational or guideline evidence with no single verified effect this pass). Each analysis below is flagged accordingly; promoted ones are marked **[Installment — see Section 2.5–2.9]**.

3.1 · How to make these analyses fully catalogue-able

The four covered Oracles work because each intervention object carries an explicit citation field next to its effect and grade (for example `evidence:{grade:"A", src:"DAPA-CKD; EMPA-KIDNEY; CREDENCE"}`). Adding the same per-intervention citation field to the remaining dashboards would let a future build extend this table to the whole Atlas with the same integrity — every row traceable, none inferred.

3.2 · All 28 analyses — promotion status and stored evidence base

Analysis	Named references / evidence base (as stored, no per-reference effect pairing)
All-Cause Mortality & Longevity [Installment — see Section 2.5–2.9]	Mandsager (Cleveland Clinic) · Kaminsky 2022 AHA (n=750,302) · GBD 2019 · Statistics Canada 2020-2022 life tables · VITAL · ASPREE · COSMOS · USPSTF 2022 · Holt-Lunstad 2010 · SELECT 2023
Longevity Fiscal Impact Model [non-interventional — cites data / model / registry, no treatment effect]	van Baal et al., PLoS Medicine 2008 · Bonneux et al., BMJ 1998 · Ontario Financial Accountability Office 2025 · Ontario 2025-26 health envelope
Life Expectancy Shift Calculator [non-interventional — cites data / model / registry, no treatment effect]	U.S. Social Security Administration Period Life Table 2022 (2025 Trustees Report)
All-Cause Dementia [Installment — see Section 2.5–2.9]	Lancet Commission 2024 · ACTIVE trial 20-yr · UK Biobank · Whitehall II · network meta-analyses
Osteoarthritis (Knee & Hip) [Installment — see Section 2.5–2.9]	Pereira 2025 NMA · GBD 2021 · UK Biobank · Cochrane reviews · Mendelian randomisation
Depression — Risk & Intervention Atlas [Installment — see Section 2.5–2.9]	Cipriani 2018 NMA · Cuijpers 2023 psychotherapy NMA · GBD 2021 · Mendelian randomisation
ADHD Negative Behavioural Outcomes [Installment — see Section 2.5–2.9]	≥280 RCTs · 14 Cochrane reviews · 8 network meta-analyses · NICE/AAP/CADDRA guidelines · Lancet Psychiatry 2025 NMA
ASD Negative Behaviours [Installment — see Section 2.5–2.9]	RUPP 2002 NEJM (risperidone) · Marcus 2009 JAACAP (aripiprazole) · Hardan 2012 (NAC) · Sandbank 2022 Project AIM (JAMA Ped) · JAMA Pediatrics 2024 (ABA dose-response, n=9,038) · Wu 2024 Front Pediatrics (exercise) · Yap 2021 Cell (microbiome) · Frye 2018 (folinic acid) · VanderWeele-Ding 2017 (E-values) · CDC 2025 (1-in-31 prevalence)
Benign Prostatic Hyperplasia [Installment — see Section 2.5–2.9]	MTOPS · CombAT · Cochrane reviews · AUA 2023 guideline · network meta-analyses 2003–2025

Analysis	Named references / evidence base (as stored, no per-reference effect pairing)
Universal Solid-Organ Transplant Mortality [Installment — see Section 2.5–2.9]	ISHLT Registry 2023 (Stehlik JHLT 2023;42:e1) · USRDS SRTR 2022 · OPTN SRTR 2022 · IPTR 2022 · UNOS 2022 · NEJM · JACC · Circulation · J Heart Lung Transplant · Am J Transplant · Pearl Causality 2nd ed. 2009 · VanderWeele & Ding Ann IM 2017
Cholesterol & Arterial Stiffness [Installment — see Section 2.5–2.9]	CTT meta-analyses · 10 RCTs · ACC.26 conference · FOURIER · ORION-10/11 · IMPROVE-IT
Pre-Eclampsia & DM199 / KLK1 Analogues [Installment — see Section 2.5–2.9]	DiaMedica DM199 Phase 1/2 · KLK1 literature · PE→CVD cohort meta-analyses
Lymphoma / Waldenström Macroglobulinemia [Installment — see Section 2.5–2.9]	ASPEN (Tam Blood 2020; JCO 2023) · iNNOVATE (Buske JCO 2022) · Gertz Am J Hematol 2023, 2025 · Pophali 2018 · Drake 2010
Bipolar II Etiology & Interventions [Installment — see Section 2.5–2.9]	STEP-BD · CANMAT 2018 · U.S. POINTER trial · 2024–2026 BD heritability literature
Parkinson's Disease Interventions [Installment — see Section 2.5–2.9]	PD literature 2002–2026 · MR studies · cohort meta-analyses
Portal Vein Thrombosis [evidence pending — observational / guideline]	AASLD guidelines · cirrhosis/PVT meta-analyses · TIPS RCTs
McCune-Albright Syndrome [evidence pending — observational / guideline]	FD/MAS Consortium guidelines (Javaid 2019, Orphanet) · Boyce JBMR 2014 · de Castro 2019 · burosumab XLH extrapolation · denosumab pediatric (giant-cell)
Cancer — Multi-Site Causal Network [Installment — see Section 2.5–2.9]	EBCTCG · Cochrane · SEER 2024 · NCCN v.2024–v.2026 · ESMO Living Guidelines · landmark RCTs (FLAURA · ADAURA · KEYNOTE · CheckMate · DESTINY · PERSEUS · CARTITUDE)
Cardiovascular Disease — Pearl SCM [Installment — see Section 2.5–2.9]	ISCHEMIA · COURAGE · PARADIGM-HF · DAPA-HF · EMPEROR · FOURIER · ODYSSEY · CTT · ARISTOTLE · ROCKET-AF · RE-LY · COMPASS · ATTR-ACT · COAPT · PARTNER · SPRINT · PREDIMED · CASTLE-AF · EAST-AFNET4 · CHA2DS2-VASc · TIMI · GRACE
Immunological Conditions, Allergies & Food Intolerances [Installment — see Section 2.5–2.9]	Cochrane allergy reviews · IBD/RA guidelines · microbiome literature · mast-cell stabiliser RCTs
Metabolic Disease (Diabetes & Metabolic Syndrome) [Installment — see Section 2.5–2.9]	ADA guidelines · UKPDS · DCCT · SELECT · LEADER · STEP · network meta-analyses
Brain — Malignancies, Injuries & Diseases [Installment — see Section 2.5–2.9]	Stupp et al. (NEJM 2005) · EF-14 TTFields · NICE-SUGAR · DAWN · DEFUSE-3 · CLARITY (Alzheimer's, MS) · LRRK2/GBA1 PD cohorts · Cochrane neuro reviews · CIBMTR · GBD 2019 neurological disorders · NCCN CNS guidelines · AAN practice parameters
US Mortality Endpoints — Infectious + Chronic Disease [Installment — see Section 2.5–2.9]	CDC NCHS 2019-2024 · Restivo 2018 (flu vaccine meta) · Moberley Cochrane 2013 (PCV) · AReSVi-006/RENOIR (RSV) · Carrat Lancet 2019 (DAA HCV) · START NEJM 2015 (ART) · iPrEx + HPTN 083 (PrEP) · Sterling NEJM 2011 (LTBI 3HP) · Seymour NEJM 2017 (SEP-1) · Huang ABATE + REDUCE MRSA · Pittet Lancet 2006 (WHO hand hygiene) · Karanika CID 2016 (stewardship) · van Nood NEJM 2013 (FMT) · CTT Lancet 2010 (statins) · SPRINT NEJM 2015 (BP) · EMPA-REG + DAPA-CKD + SELECT (SGLT2/GLP-1) · Clarity AD + TRAILBLAZER-ALZ2 (anti-amyloid) · NLST + NordICC + Marmot 2013 (screening)
Self-Caused Mortality — Overdose, Suicide, Unintentional Injury [Installment — see Section 2.5–2.9]	Sordo 2017 BMJ + Larochelle 2018 (MOUD) · Walley 2013 BMJ (naloxone) · Marshall 2011 Lancet (SCS) · Cipriani 2013 BMJ (lithium) · Anglemyer 2014 (firearm storage) · Meltzer 2003 (clozapine InterSePT) · Gibbons 2012 (SSRI) · Stanley 2018 JAMA Psych (SPI) · Brown 2005 JAMA (CBT) · Gould 2007 (crisis line) · Yip 2012 Lancet (method restriction) · Cummings 2003 (seatbelt) · Liu 2008 Cochrane (helmet) · Fell 2017 (BAC interlock) · Cicchino 2017 IIHS (ADAS) · Sherrington 2019 Cochrane (Otago) · Thompson 2000 Cochrane (pool fencing) · Runyan 1992 (smoke alarm)

Analysis	Named references / evidence base (as stored, no per-reference effect pairing)
Rare Disease — Pareto Risk-Reduction Targeting **[Installment — see Section 2.5–2.9]**	FDA orphan-drug designations · NORD rare-disease registry · Cochrane meta-analyses for hematologic malignancies · TRAILBLAZER + IPF nintedanib/pirfenidone trials · Sickle Cell Disease curative gene therapy trials (Casgevy, Lyfgenia) · CFTR modulator trials (Kalydeco, Trikafta) · NCCN oncology guidelines · ALSFRS riluzole/edaravone evidence base
Atlas Coverage of US Mortality — Deduplicated Count **[non-interventional — cites data / model / registry, no treatment effect]**	CDC NVSR vol. 74 no. 10 — Tejada-Vera et al., 'Deaths: Leading Causes for 2023' (Sep 2025) · CDC FastStats 2024 'Leading Causes of Death' · CDC NCHS Data Brief No. 549 (Drug Overdose 2024) · CDC Mortality Dashboard (Parkinson G20-G21, Influenza+pneumonia J09-J18) · Atlas data.js v3.25
Anxiety **[Installment — see Section 2.5–2.9]**	Anxiety/insomnia meta-analyses 2022–2025 across age bands · CBT-I RCTs · Tai Chi & mind-body NMAs · light-therapy trials · supplement RCTs (e.g. magnesium, L-theanine, ashwagandha, glycine)
MIMIC-III Mortality Harness **[non-interventional — cites data / model / registry, no treatment effect]**	MIMIC-III demo (100 ICU patients · 129 admissions; MIT-LCP / Beth Israel Deaconess) · representative mortality hazard ratios from atlas dashboards · approximate Canadian period life tables

3.3 · Caveats on the covered rows

(1) For Pulmonary, Kidney and Liver the “Reference(s)” cell often lists several trials that jointly support one intervention's effect; the effect size belongs to the intervention, not to any single named trial in the set. (2) The Liver Oracle's source field sometimes embeds a short result phrase alongside the citation; it is reproduced as stored. (3) Endpoints differ within and across Oracles and must not be summed or compared head-to-head. (4) Ratings reflect each dashboard's stored grade (or its GRADE word mapped via Section 1.3); where a dashboard's grade looks generous relative to the four-axis rubric — e.g. an observational cohort graded B — the stored grade is shown unchanged rather than silently re-scored, and such cases are flagged in the relevant Oracle's own antithesis section. This is an evidence-synthesis catalogue, not medical advice.