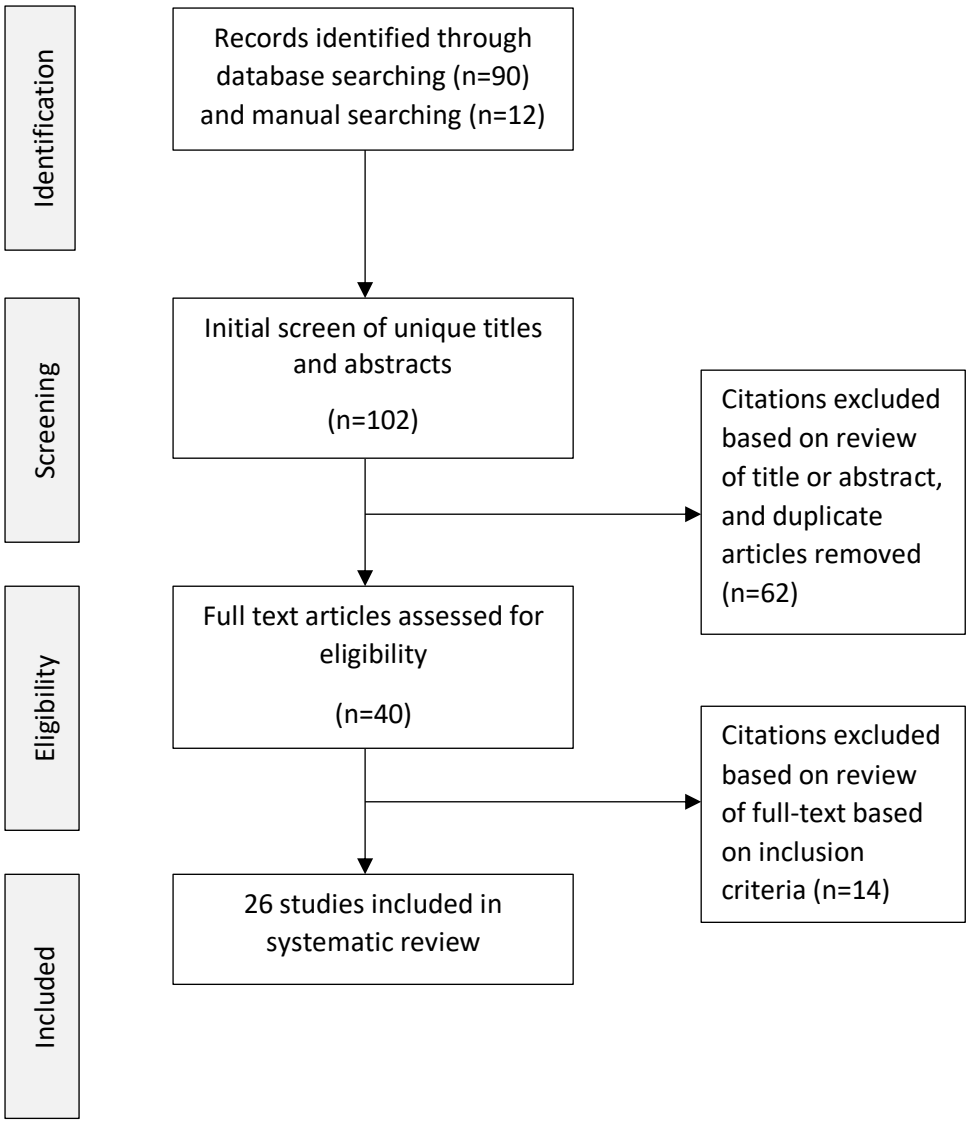

Supplementary Figure 1. Flowchart of the process of identifying and selecting included studies. The grey boxes indicate the stage of the selection process; n denotes the number of articles included at each stage of the process.

Supplementary Table 1. Data extracted from included studies.

		Study Design							Baseline Characteristics					
Reference number	Authors/ year	Study drug(s)	Study design - Reported	Inclusion Criteria	Exclusion Criteria	Patient enrollment	Drug, dosage, injection frequency and other therapeutic interventions (including description of parameters used for defining schedule of treatment)	Treatment Regimen (fixed, PRN, T&E etc.)	Mean/ SD age of patients (yr)	Gender ratio (Female %)	Previous anti-VEGF treatments/ response	Baseline CNV lesion type (%)	Baseline central retinal thickness (CRT) (μm)	Baseline visual acuity LogMAR letters; (Mean / SD)
1	Gupta et al. 2011	Ranibizumab	Retrospective	(1) Treatment naïve nAMD initiated on ranibizumab, (2) completed at least 12 months follow-up, (3) eyes with subfoveal CNV secondary to AMD of any lesion subtype with lesion size of less than 12 disc areas and VA between 24-73 logMAR letters	(1) CNV secondary to causes other than AMD, (2) lesions previously treated with laser photocoagulation, intravitreal triamcinolone, intravitreal bevacizumab or photodynamic therapy	2010 and earlier	Ranibizumab (0.5mg/0.05ml) using either loading dose or PRN; Both loading dose and PRN groups received intravitreal ranibizumab at baseline. Loading dose received 2 further consecutive monthly ranibizumab independent of clinical findings, then further injections were determined by the same re-treatment criteria as patients on PRN schedule from baseline. 1 month was defined as an interval of 30 +/- 10 days	PRN with and without loading	Loading dose group: 81.4 ± 5.9; PRN group: 81.9 ± 6.0	64.1% overall. 66.0% in loading dose group. 61.3% in PRN group.	None	LD regimen - classic/predominantly classic 27.66%, minimally classic 21.28%, occult 51.06%. PRN regimen - classic/predominantly classic 16.13%, minimally classic 32.26%. Occult 51.61%	NR	LD group: 48 ± 15.3, PRN group 44.5 ± 15.4
2	Kumar et al. 2011	Ranibizumab	Prospective	1. >50 years 2. BCVA >=25 letters 3. nAMD lesions, any component of which extended to with 200 μm of foveal center 4. Signs of presumed recent disease progression in cases with occult or minimally classic lesions, as defined by recent loss of vision, new hemorrhage and/or an increase in lesion size on fluorescein angiography.	Nil	2010 and earlier	Monthly 0.5 mg ranibizumab for the first 3 months. Retreatment criteria were not prescriptive and the decision to retreat was based on individual clinician's judgement. Retreatment was considered if there was any deterioration in the signs and symptoms including drop in BCVA (5 to 19 letters from baseline), worsening of IRF or SRF, fresh hemorrhage or extension of lesion on FA. It was recommended that retreatment be avoided if there was: no improvement in BCVA; persistent resolving IRF and SRF; evidence of structural damage on OCT; or an adverse event such as drop in BCVA by >20 letters. In patients with clinical evidence of irreversible damage with no potential benefit from continuing treatment, a decision was taken to suspend further intervention.	PRN	79.5 (range 61-95)	60.4%	None	Classic no occult 34%, predominantly classic 22%, minimally classic with occult 9%, minimally classic without occult 4%, occult no classic 19%, RAP 12%	347 μm ± 102	49.5 (13.4)
3	Shona et al. 2011	Ranibizumab	Retrospective	1. Initiated on ranibizumab with at least 12-month follow-up 2. To initiate ranibizumab: VA requirements of 24–73 logMAR letters with demonstrable disease progression and no central irreversible structural damage. All lesion subtypes with lesion size of 12 disc areas or less were included.	1. Patients with choroidal neovascularization secondary to causes other than AMD 2. Lesions previously treated with laser photo coagulation, intravitreal triamcinolone, intravitreal bevacizumab or photodynamic therapy	2010 and earlier	All patients received a loading dose of 3 consecutive monthly ranibizumab injections; criteria for retreatment were persistence or recurrence of any SRF/IRF on OCT in a previously dry macula, increase or new SRF/IRF on OCT, decrease of 5 letters in VA associated with fluid on OCT, new subretinal or intraretinal hemorrhage and/or angiographic evidence of increase in lesion size.	PRN	Poor: 82.2 (9.2) Intermediate: 82.9 (5.5) Good: 79.9 (8.0)	Poor: 59.3% Intermediate: 60.6% Good: 59.3%	None	Poor: occult 41%, minimally classic 26%, classic 33%; Intermediate: occult 39%, minimally classic 9%, classic 52% Good: occult 56%, minimally classic 18%, classic 26%	NR	Poor: 28.9 (4.7) Intermediate: 43.8 (4.7) Good: 61.7 (61.7)
4	Pushpoth et al. 2012	Ranibizumab	Retrospective	Meet eligibility criteria as per the Royal College of Ophthalmologists Guidelines	Nil	2007 to 2009	Treatment strategy following ProNTO guidelines. There were 3 loading doses of ranibizumab, followed by monthly follow-up. Any patients who showed signs of disease activity were advised to have further treatment. Disease activity defined as one/more of: any fluid as detected by OCT (if the profile of the fluid spaces had not altered for 3 visits in the second or more years of follow-up then treatment might be missed), retinal hemorrhage or reported distortion.	PRN	75±8.4	65.50%	Group 1 - had pretreatment (n=181) and were excluded from this analysis	Majority (59.76%) had occult choroidal neovascularisation, 28.55% had minimal or predominantly classic and 11.69% retinal angiomatous proliferation	NR	Group 2 - 54.1 ± 15.3
5	Muniraju et al. 2013	Ranibizumab	Retrospective	Consecutive patients with nAMD who were initiated on ranibizumab therapy were identified from the ranibizumab in NV-AMD database. Eyes with subfoveal choroidal neovascularization secondary to AMD of any lesion subtype with lesion size of less than 12 disc areas with no permanent central damage and baseline VA between 24 and 73 logMAR letters were included.	Patients with choroidal neovascularization secondary to causes other than AMD, lesions previously treated with laser photocoagulation, intravitreal triamcinolone, intravitreal bevacizumab or photodynamic therapy and patients who did not complete the 3-year follow-up.	2008 to 2010	The loading dose of 0.5 mg ranibizumab during 3 consecutive months was mandated. Further injections were given if the retreatment criteria were met and at the discretion of the treating clinician. Criteria for retreatment were mainly based on findings detected on OCT, including persistence, increase or new SRF and intraretinal oedema on OCT, decrease in VA associated with fluid on OCT, and subretinal or intraretinal hemorrhage. If the clinician decided to discontinue treatment, the patient was followed up as required and not monthly. Discontinuation criteria included continuous deterioration or no improvement in VA compared to baseline at the 6-month follow-up, persistent subretinal and/or intraretinal fluid with no response to treatment or evidence of subfoveal structural damage on OCT and at the discretion of the treating physician.	PRN	82.7 (range 55–97)	67%	None	NR	NR	48.2 (16.9)
6	Tan et al. 2013	Ranibizumab	Retrospective	Included patients with nAMD of all lesion subtypes who had not previously received treatment and who completed at least 12 months of follow-up and where there was recordable BCVA at baseline, and months 3, 6, 9 and 12.	Excluded patients whose treatment was terminated prematurely due to side-effects, other systemic co-morbidities, and patient choice	2007 to 2009	Each patient received an initial set of 3 ranibizumab 0.5 mg injections at monthly intervals. Subsequent injections were given if indicated based on clinical finding of worsening BCVA and OCT findings of persistent hemorrhage or fluid. Where treatment was not warranted, patients were reviewed at clinic at 1 to 2 month intervals.	PRN	78.5 (7.0)	67.6%	None	NR	NR	NR
7	Ross et al. 2013	Ranibizumab	Prospective	Treatment naïve first-eligible eyes with nAMD and a presenting VA of 23 or more letters, treated within a large public hospital serving a geographically defined area of the United Kingdom	Prior treatment with ranibizumab or bevacizumab privately, and prior or concurrent photodynamic therapy, thermal laser therapy, or gas injections for nAMD, peripapillary lesions, extrafoveal lesions, or baseline VA of <23 logMAR letters, the lower limit for NHS funding for ranibizumab. Patients with follow-up of less than 1 year.	2007 to 2010	Loading phase of 3 consecutive monthly injections. Retreatment with ranibizumab was performed if any of the following criteria was fulfilled in subsequent monthly assessments: >20% increase in central 1mm retinal thickness since last visit on OCT, presence or qualitative increase in the amount of intraretinal/subretinal fluid on OCT, or appearance of new macular hemorrhage on fundal examination with or without a decrease in VA. If the intraretinal fluid or subretinal fluid persisted despite numerous injections, then treatment was stopped but was restarted if there was a qualitative deterioration.	PRN	Median = 82.3 (IQR 76.9 - 86.3)	66.3%	None	70.9% minimally classic/occult no classic CNV, 27.8% classic no occult/predominantly classic CNV, 1.2% FFA unassessable/not performed	353 μm ± 102	54.4 ± 14.2
8	Chavan et al. 2014	Ranibizumab	Retrospective	Confirmation of nAMD was based on presence of drusen or age-related changes in the retinal epithelium on OCT and late-phase leakage on FA of subfoveal choroidal neovascularization with either classic, occult, or retinal angiomatous proliferative components. Eyes with nAMD and visual acuity of 6/12 to 6/96 were considered to satisfy the NICE guidance criteria	Patients were excluded from this survey if they had no follow-up after baseline injection or were recruited into a clinical trial. Eyes were excluded if they had any photodynamic therapy (PDT), lesions secondary to non-AMD causes, serious detachments of pigment epithelium, peripapillary lesion, or choroidal polyps.	2009	Loading dose of 3 injections followed by retreatment on a PRN basis. Using a 2-stop model, repeat injections were scheduled shortly after monitoring visits if lesions were found to be active. As much as possible, monitoring visits were scheduled every month. Retreatment decision was OCT-guided and was performed until no further reduction in intra or SRF could be achieved. In accordance with retreatment protocols used in earlier ranibizumab PRN studies such as the PRONTO study, we did not specifically continue repeat injections to attempt to resolve PEDs which were not associated with presence of subretinal or IRF on OCT. Patients could be discharged from follow-up in the treatment program if they had not required retreatment in over 12 months or if it was felt that benefit could not be gained due to extensive macular damage.	PRN	81.8±6.7 (range: 65–95)	62.5%	None	Occult 56%, classic containing 38%, and RAP 6%	423 μm ± 115	Year 1: 52.3±14.7 Year 2: 52.4±14.6 Year 3: 52.9±14.6
9	UK AMD EMR. 2014	Ranibizumab	Retrospective	1. Treatment-naïve 2. Treated with ranibizumab for nAMD	1. Treatment with combined therapy or bevacizumab at any time point	2012 and earlier	Loading phase of 3 ranibizumab monthly injections and PRN retreatment regimen	PRN	79.7 (median 81; range 55-108) (IQR 75-85)	63%	None	NR	NR	55
10	Basheer et al. 2015	Ranibizumab	Prospective	1. Receiving ranibizumab for wAMD 2. Gave consent 3. >=50 years 4. VA between 0.00 and 2.30 logMAR 5. Presence in study eye of previously untreated active CNVM	1. Previous treatment 2. Transferred to another trust 3. Subsequently had another diagnosis (dropped from analysis) 4. Received no more than three treatments in the loading phase (dropped from analysis)	2007 to 2012	Loading phase of 3 Ranibizumab 0.5mg monthly injections (all patients) Following this, patients were monitored monthly and the following retreatment criteria were used to establish whether further treatment was required: Loss of letters with fluid on OCT; any fluid on OCT – intraretinal fluid, subretinal fluid; Increased size of pigment epithelial detachment; new retinal hemorrhage; new CNVM. In addition, if FFA revealed active CNVM, treatment was repeated each month for three months. Treatment was further individualized by sequentially lengthening follow-up intervals when a period of stability had been established.	PRN	83	49%	None	NR	NR	35
11	Borooah et al. 2015	Ranibizumab	Retrospective	Patients were enrolled if they had started treatment prior to September 2008 with the potential for 5 years of follow-up data.	Patients who had previously been treated with photodynamic therapy were excluded in order to compare outcomes to those of the clinical trials.	2007 to 2008	The normal treatment regimen in the clinic initially involved 3 ranibizumab monthly treatments. Patients were then followed-up on a 4–8 weekly basis. Retreatment was administered if there was recurrence noted on clinical examination or OCT.	PRN	76.5	60%	NR	Pure classic 9.6%, predominantly classic 16.4%, minimally classic 8.7%, occult 36.5%, RAP 24.0%	NR	0.58 +/- 0.28
12	Williams et al. 2015	Ranibizumab	Prospective	1. Receiving ranibizumab for nAMD of all types for 12 or more months at the unit	1. Alternate diagnoses 2. Received prior photodynamic therapy	From 2007	"The policy in our department is not to vary appointment times based on patient response until the second year of treatment".	PRN	NR	NR	None	NR	NR	53
13	Buckle et al. 2016	Ranibizumab	Prospective	Treatment-naive eyes with a presenting visual acuity (VA) of 23 letters or more	Exclusion criteria included: prior treatment with ranibizumab or bevacizumab privately, prior or concurrent photodynamic therapy, VA<23 logMAR letters at baseline, and failure to complete the loading phase of injections.	2007 to 2013	PRN treatment posology after an initial loading phase of 3 ranibizumab injections at monthly intervals. Patients are followed up at monthly intervals with SD OCT and fundal examination until no injections have been required to either eye for 6 months, after which follow-up intervals are gradually extended. If no injections have been required for 1 year patients are discharged and advised to return if they notice any new symptoms of blurring or distortion of vision in either eye.	PRN	82.5	64.9%	None	NR	327 μm	56.6
14	Razi et al. 2016	Ranibizumab	Retrospective	1. Diagnosed with CNV for a minimum of 3 years 2. Lesion size <=12 disc areas with absence of permanent damage to central fovea 3. Received at least one cycle of ranibizumab 4. Underwent OCT during each assessment to confirm diagnosis 5. Seen and followed by a medical retina consultant	1. wAMD had previously been treated with alternative therapies (e.g., PDT, anti-VEGF) 2. Received ranibizumab for other diagnoses 3. Did not complete the 3-year follow-up period	NR	Ranibizumab 0.5 mg on a monthly basis for 3 consecutive months. After the 3rd mandatory injection, patients were followed up as outpatients once a month, throughout the 3-year follow-up period. Patients received further injections PRN if retreatment criteria were met or at the discretion of the treating clinician.	PRN	81.9 (range 61-93)	53%	None	Occult 57%, minimally classic 26%, predominantly classic 17%	NR	37.3 (range 4 to 68)
15	Talks et al. 2017	Aflibercept	Retrospective	Treatment-naïve eyes in which aflibercept treatment with a minimum of 1 year of follow-up	Nil	2013 to 2015	Use of aflibercept following the VIEW protocol; 3 injections 1 month apart and then 2 monthly for the first year.	Fixed	80.0 (8.3)	63%	None	NR	NR	53.7 (SE: 0.4)
16	Almuhtaseb et al. 2017a	Aflibercept	Retrospective	Patients were treatment naïve diagnosed with neovascular age-related macular degeneration (nAMD) who received aflibercept over 1 year per the VIEW 1 and VIEW 2 Clinical Trials' protocol.	Nil	NR	Aflibercept over 1 year as per the VIEW 1 and VIEW 2 Clinical Trials' protocol; 3 consecutive monthly aflibercept intravitreal injections (Q4W) followed by continuous bimonthly fixed-interval dosing injections for the rest of year 1 (Q8W).	Fixed	82	72%	None	NR	311 μm	52 (range 25 to 70)
17	Almuhtaseb et al. 2017b	Aflibercept	Retrospective	All treatment-naive eyes who were initiated on treatment for nAMD with aflibercept, received aflibercept according to the VIEW 1&2 Clinical Trials' protocol during the first year of treatment and finished year 2 of treatment with aflibercept prior to the data cut-off point.	Results from eyes whose treatment did not follow the VIEW protocol during year 1 were excluded.	2016 and earlier	Eyes following the VIEW protocol during year 1 were defined as eyes having received 7 or 8 injections in the time period up to and including wk 56 (from baseline injection). Results from eyes whose treatment did not follow the VIEW protocol during year 1 was excluded. Eyes were stratified empirically according to the number of injections received in the 2nd year into 3 different groups, which are as follows: Group A, 0–3; Group B, 4–5, Group C, 6 or more.	Year 1: Fixed Year 2: Variable, fixed or PRN	82	68%	None	NR	NR	56.3
18a	Lee et al. 2017	Ranibizumab	Retrospective	Treatment naive eyes with the diagnosis of nAMD. The eyes were required to have at least 1 year of follow-up data as well as treatment monotherapy with either ranibizumab or aflibercept.	Nil	Mean year starting treatment 2013	Ranibizumab 3 loading doses plus PRN	Ranibizumab: PRN	NR	63.5%	None	NR	NR	55.0 (15.6)
18b	Lee et al. 2017	Aflibercept	Retrospective	Treatment naive eyes with the diagnosis of nAMD. The eyes were required to have at least 1 year of follow-up data as well as treatment monotherapy with either ranibizumab or aflibercept.	Nil	Mean year starting treatment 2014	Aflibercept 3 loading doses at monthly intervals and then fixed 2 monthly for the first year, or treat and extend.	Aflibercept: Fixed or T&E	NR	63.5%	None	NR	NR	54.9 (16.0)
19	Vardarinos et al. 2017	Ranibizumab	Retrospective	For newly diagnosed patients diagnosed with nAMD who were offered ranibizumab	Nil	2013 to 2014	Monthly injections, every 28 days until a dry macula was evident on SD-OCT. Once that was achieved, the injections continued, incrementally increasing the treatment intervals by 2 weeks until a maximum interval of 12 weeks provided there were no signs of recurrence of disease activity on SD-OCT or BCVA loss of more than 5 letters which could not be explained by other ophthalmic conditions. In case of a recurrence the treatment interval was reduced by 2 weeks. Signs of disease activity on SD-OCT were considered to be the presence of IRF and/or SRF and/or retinal/sub-retinal hemorrhage. In the 2nd year of treatment, for patients who achieved repeated treatment intervals of 12 weeks and on the review visit, the condition was considered inactive (no IRF or SRF, no hemorrhage, no BCVA loss compared to last visit) the patients were given the option to be placed on a T&E regime, where they would be reviewed with an SD-OCT on incrementally increasing intervals (2–3 wk at a time) and would be offered an injection only if there was disease recurrence.	T&E	80.9 (8.8)	67%	None	NR	384.6 μm (154.9)	60.5 (8.9)
20	Yang et al. 2017	Ranibizumab	Retrospective and Prospective	Eligibility criteria: (1) adult patients ≥50 years of age with active choroidal neovascularisation secondary to AMD in one or both eyes at the time of diagnosis; (2) medical records providing at least 12 months of retrospective data on either the ranibizumab PRN regimen prior to switching to T&E (prior PRN cohort), or the T&E regimen (anti-VEGF-naive cohort) immediately prior to enrolment.	No prior treatment with an anti-VEGF agent (i.e. bevacizumab or aflibercept) other than ranibizumab in the study eye (defined as the eye first treated with a T&E regimen)	2016 to 2017	Two cohorts - (1) those switching from PRN to a TAE regimen ('prior PRN'), (2) initiating TAE as first anti-VEGF therapy ('anti-VEGF-naïve'). Only Cohort 2 data included in this analysis. Patients were treated according to routine medical practice and local prescribing information based on the licensed ranibizumab posology. For T&E - this is monthly injection until maximum VA is achieved and/or there are no signs of disease activity (i.e. no change in VA, OCT, and other signs/symptoms of disease).	T&E	Anti-VEGF-naïve cohort 77.5 (7.6)	Overall 62.5%. Prior PRN cohort = 52.9%. Anti-VEGF-naïve cohort = 65.5%	Prior PRN cohort were excluded from this analysis.	NR	Anti-VEGF-naïve cohort: 365 μm (105).	Anti-VEGF-naïve cohort: 58.5 (16.9)
21	Ozturk et al. 2018	Aflibercept	Retrospective	Receiving aflibercept for nAMD for at least 1 year; treatment naïve eyes	Nil	2016 to 2017	Aflibercept as per "VIEW protocol"	Fixed	7 or less IVI group: 82.6 (7.3); 8 IVI group: 78.8 (7.4)	7 or less group: 57.1%, 8 IVI group: 52.4%	None	For 7 or less IVI group: 47.6% occult, 42.9% minimally classic, 4.8% predominantly classic, 4.8% other; for 8 IVI group: 38.1% occult, 38.1% minimally classic, 23.8% predominantly classic, 0% other	NR	Median: 47.0 (Q1 43.0, Q3 55.0) for 8 IVI group; 57.0 (Q1 50.0, Q3 62.0) for 7 or less IVI group
22	Eleftheriadou et al. 2018	Aflibercept	Retrospective	Consecutively treated eyes of patients with nAMD. Treatment naïve eyes receiving intravitreal aflibercept injections.	Any exclusions were recorded using a consolidated standards of reporting trials-like approach to minimise bias.	2013 to 2014	nAMD treatment guidance protocol for aflibercept developed by Moorfields Eye Hospital. These are similar to guidelines developed by clinicians in the UK and broadly based on using fixed dosing in the first year of treatment followed by a T&E regimen.	Fixed + T&E	80.6 ± 8.3	58.90%	None	CNV morphology included a class component 22.5%, purely occult 65.9%	351 μm	54.4 ± 16
23	Fulcher et al. 2019	Aflibercept	Retrospective	Diagnosed with nAMD. Completed 1 year of follow-up.	Insufficient data (missing visits, less than 12 months of data), missed loading dose injections, incorrect diagnosis, the use of different optical coherence tomography (OCT) machines across visits, ocular co-morbidities that may impact on results (e.g. uveitis), or treatment with ranibizumab. Patients with controlled glaucoma or ocular hypertension (n = 4) were eligible for inclusion.	2014 to 2016	Each eligible eye received three loading dose injections at four-weekly (±1 week) intervals. For the remaining 12-month follow-up period, further injections were administered using a 'treat and extend' protocol, in which injections were given at each visit, and follow-ups were determined based on findings from OCT, VA and clinical examination	T&E	79 (9)	51%	None	Number with classic lesion 7 (9.7%) Number with idiopathic polypoidal choroidal vasculopathy (IPCV) and occult lesion 7 (9.7%) Number with minimally classic lesion 9 (12.5%) Number with occult lesion 31 (43.1%) Number with predominantly classic lesion 8 (11.1%) Number with retinal angiomatous proliferation (RAP) lesion 10 (13.9%)	421 μm ± 123	55.4 ± 15.5
24	Fasler et al. 2019	Ranibizumab, Aflibercept	Retrospective	≥1 ranibizumab or aflibercept injection, entry of 'AMD' in the diagnosis field of the EMR and a minimum of 1 year of follow-up	(1) unknown date of first injection, (2) treatment outside of routine clinical care before the first recorded injection in the database, including pegaptanib, previous laser or photodynamic therapy, bevacizumab	2007 to 2018	Ranibizumab or aflibercept; NR - dosage/frequency	NR	78 (95%CI 77.7-78.3)	61%	None	NR	NR	56.2 (95%CI 55.6-56.8)
25	Horner et al. 2019	Ranibizumab	Retrospective	Consecutive, treatment naïve patients with confirmed diagnosis of active nAMD from Jan-Dec 2009. and commenced on anti-VEGF treatment with a full follow-up of eight years	Other causes of choroidal vascular membranes e.g. myopic CNVM or peripapillary CNVM	2009	Standard loading dose of 3 intravitreal injections of 0.5mg ranibizumab at 4 weekly intervals. Retreatment was decided by assessing clinicians based on the evidence of disease activity (presence of intraretinal fluid or subretinal fluid on OCT scans, macular hemorrhage or exudation). All pts were reassessed at 4 weekly intervals for the first 6 months and extended to 8 weekly reviews if disease remained inactive.	PRN	Median age of those who completed 8 years follow-up: 72 (IQR 67-76)	For those who completed 8yrs follow-up: 66%	None	NR	NR	Median VA 61.1 (IQR: 46.1-69.9)
26	Chandra et al. 2020	Aflibercept	Retrospective	Treatment-naïve patients	If they received any other anti-angiogenic agents at any time point before or after initiation of aflibercept therapy	2013 to 2014	Aflibercept - injection frequency as per treatment regimen. No other therapeutic interventions. Recommended protocol was 3x loading doses followed by 8 weekly fixed dosing until week 40 --> then transferred to T&E. When patients are injected at 12 weekly intervals for 3 consecutive patients, they could be referred to a stable AMD retinal clinic where they are monitored at 8-12 weekly intervals --> then PRN or combination of T&E/PRN.	Fixed + T&E	79 ± 8.5	54%	None	NR	NR	58.3 ± 15.4

	Results															
Reference number	Sample size (patients)	Sample size (eyes)	Follow-up duration	Number of intravitreal injections administered (mean/median/SD)	Number of visits (mean/median/SD)	Mean BCVA gain (SD) at 12 months (logMAR letters)	Percentage of patients with >15 letters gained or lost at 12 months	Mean BCVA gain (SD) at 24 months	Percentage of patients with >15 letters gained or lost at 24 months	Mean BCVA gain (SD) at timepoints longer than 24 months	Percentage of patients with >15 letters gained or lost at timepoints longer than 24 months	Proportion of eyes with 6/12 (70 logMAR letters) or better vision at Baseline and 1 year, 2 years, 3 years, study end	Vision related QoL	Change in CRT (μm) (mean/median/SD)	Percentage dry (at follow up)	Adverse events (Intraocular inflammation: uveitis, vitritis, vasculitis, endophthalmitis. Raised IOP. Cardiovascular events)
1	78	78	> 1 year	LD group 6.0, PRN group - 4.5	NR	LD group 4.4, PRN group 4.0	LD group 29.8%, PRN group 12.9%.	NR	NR	NR	NR	NR	NR	LD group -38 μm, PRN group -44 μm	NR	1 patient developed acute anterior uveitis. 0 endophthalmitis.
2	81	81	1 year	Mean 5.6 (2.3)	NR	3.7 (10.8)	>=15 letters BCVA gained: 17.1% >15 letters BCVA lost: 2.5%	NR	NR	NR	NR	NR	NR	Mean CFT: at 3 months 231μm (80), at 6 months 248μm (102), at 12 months 246μm (107).	NR	1 patient had raised IOP.
3	87	87	1 year	12 months: Overall: 5.7 Poor: 5.3 Intermediate: 6.12 Good: 5.70	NR	Poor: 14.0 Intermediate: 7.1 Good: 2.9	Gain >15 letters Poor: 45% Intermediate: 30% Good: 15% loss>15 letters Poor: 4% Intermediate: 5% Good: 4%	NR	NR	NR	NR	NR	NR	Mean CMT change: at 12 months: Poor: -133 μm Intermediate: -49 μm Good: -45.59	NR	No case of endophthalmitis, retinal detachment or acute inflammation.
4	1017	1086	4 years	Group 2: 12 months: 5.2 ± 2.7; 24 months: 8.3 ± 3.7; 36 months 10.8 ± 5.8; 48 months: 12.8 ± 7.8	NR	Group 2: 3.8	Group 2: Gain: 20.1% Loss: 9.5%	Group 2: 2.4	Group 2: Gain: 20.1% Loss: 14.6%	Group 2 BCVA at 36 months = 54.3 ± 18.1; at 48 months = 58.7 ± 17.2	36 months - Group 2: Gain: 18.1% Loss: 18.8%	Group 1 and 2 Baseline: 6.4% >75 letters Year 1: 31.3% >75 letters Year 2: 17.2% >75 letters Year 3: 12.7% > 75 letters Year 4: 14.6% > 75 letters	NR	NR	NR	4 cases of presumed endophthalmitis from 1086 eyes.
5	156	174	> 3 years	Mean: Year 1: 4.8 (2.2) Total by end of Year 2: 7.8 (4.2) (2.9 injections in 2nd year) Total by end of Year 3: 10.2 (6.2) (2.4 injections in 3rd year)	NR	3	Gain: 20.1% Loss: 9.8%	2.2	Gain: 20.7% Loss: 14.4%	NR	36 months: Gain: 19% Loss: 19%	NR	NR	NR	NR	NR
6	71	71	> 1 year	Mean 5.4 (1.9)	NR	0.3	Gain: 15.0%	NR	NR	NR	NR	Baseline: 9.8% Year 1: 22.5%	NR	NR	NR	NR
7	406	406	> 1 year	First year = 5.9 (range 3-13), Second year = 3.6 (range 0-10)	First year = 12.2 (range 7-14); Second year = 10.6 (range 4-13)	4.1 ± 14.2	NR	1.6 ±17.6	NR	NR	NR	NR	NR	Year 1 = -98 μm; Year 2 = -78 μm	NR	2 endophthalmitis cases (rate of 1 in every 1828 injections; 1 in every 203 eyes)
8	117	130	3 years	Mean (range) Year 1: 5.9 (1–11) Year 2: 4.1 (0–10) yr 3: 4.21 (0–11)	Mean (range) Year 1: 12.3 (7–18) Year 2: 10.6 (3–18) Year 3: 11.5 (1–17)	−1.34±15.34	Gain: 13%	−2.4±17.4	Gain: 12.3%	Year 3: −1.7±17.8	Gain: 16.8%	Note values relate to >75 logMAR letters Baseline: 3.3% Year 1: 6.7% Year 2: 7.9% Year 3: 10.1%	NR	Mean CRT Year 1: 325 μm ±79, Year 2: 331 μm ±88, Year 3: 325 μm ±98	NR	NR
9	11135	12951	3 years	Year 1: 5.7 (median 6, range 1-13) Year 2: 3.7 (median 4, range 0-13) Year 3: 3.7 (median 4, range 0-12)	Year 1: 9.2 Year 2: 8.2 Year 3: 8.2	2	Available graphically	1	Available graphically	Year 3: -2	Available graphically	NR	NR	NR	NR	NR
10	106	123	2 years	0-12 months: 6 (range 3 to 12) 12-24 months: 4 (range 1 to 12)	NR	3.5	Loss <15 letters: 91.8% Gain >=15 letters: 20.3% Loss >15 letters: 8.1%	3	Loss <15 letters: 88.6% Gain >=15 letters: 19.7% Loss >15 letters: 11.5%	NR	NR	NR	NR	NR	NR	NR
11	96	104	Mean > 4 years	Mean 9.6 ±6.5 per patient over follow up. 2.4 injections per patient per year.	Year 1: 7.8±3.3, Year 2: 4.8±3.4, Year 3: 3.9±3.6, Year 4: 2.0 ±2.6, Year 5: 0.4 ± 1.2	NR	NR	NR	NR	NR	Over mean follow-up of 4 years and 1 month. 9.6% gained ≥15 letters 24.0% lost ≥ 15 letters	NR	NR	NR	NR	1 vitreous hemorrhage, 0 endophthalmitis, 1 corneal abrasion
12	708	805	1 year	First year: 5.9	NR	4.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
13	1'278	1'483	< 5 years	Mean Year 1: 6.0; Year 2: 3.2; Year 3: 2.8; Year 4: 2.3; Year 5: 1.5	Median number of hospital visits per patient completing year 1 was 14 and in years 2, 3, 4 and 5 the median was 13 visits each year	NR	For eyes with a baseline VA of ≤70 logMAR letters, 15 letter gain was achieved by 184 (16.8%) eyes. For all eyes, there was 15 letter loss in 126 (9.7%) eyes.	NR	For eyes with a baseline VA of ≤70 logMAR letters, gain was achieved by 137 (18.8%) For all eyes, there was 15 letter loss in 111 (12.9%) eyes	NR	For eyes with a baseline VA of ≤70 logMAR letters, gain >15 letters was achieved by 70 (15.9%), 39 (15.5%) and 8 (8.2%) eyes in yr 3–5, respectively. Loss of >15 letters: Year 3 107 (21.1%); Year 4 64 (22.4%); Year 5 30 (27.5%)	Baseline: 16.9% Year 1: 17.0% Year 2: 15.9% Year 3: 15.6% Year 4: 14.9%	NR	The mean CRT at year 1, 2, 3, 4 and 5 were 261, 257, 257, 248 and 248 μm, respectively.	NR	8 eyes (0.5%): Endophthalmitis A total of 16 993 injections were administered to the 1483 eyes which provides an estimate of the endophthalmitis rate per injection of 1 in 2124 injections. Subconjunctival hemorrhage (31 eyes; 2.1%) IOP >21 mm Hg (40 eyes; 2.7%), subconjunctival hemorrhage (31 eyes; 2.1%) and corneal epithelial abrasion (26 eyes; 1.8%)
14	70	76	3 years	Year 1: 5.6 (range 3 to 9), Year 2: 3.5 (range 0 to 8), Year 3: 3.5 (range 0 to 10)	NR	NR	>=15 letters gained: 34%	NR	>=15 letters gained: 30%	36 months: 5.3 letters	36 months: >=15 letters gain: 29% >15 letters loss: 8%	NR	NR	NR	NR	None
15	1682	1840	1 year	Mean: 7	Mean: 7.3	5.1	Gain: 18% Loss: 8%	NR	NR	NR	NR	Baseline: 16.4% Year 1: 33.7%	NR	NR	NR	NR
16	223	255	1 year	Mean: 7	1 baseline visit and 2 follow up clinician visits with fixed injection appointments in year 1.	8	NR	NR	NR	NR	NR	NR	NR	Mean CRT: at month 5 = 235μm, at month 11 = 211μm.	At month 11, 136 eyes (53%) were inactive (dry), whereas 119 eyes (47%) remained active(wet).	NR
17	1'083	1'180	2 years	Mean 3.7 in the 2nd year	NR	Not included in the 12 month analysis to avoid duplication of data. Mean gain in VA = 5 letters	NR	2.8	NR	NR	NR	NR	NR	NR	NR	NR
18a	942	942	1 year	Ranibizumab: 5.8	Ranibizumab: 10.8	Ranibizumab: 1.6 (95% CI 0.5 to 2.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
18b	942	942	1 year	Aflibercept: 7.0	Aflibercept: 8.9	Aflibercept: 6.1 (95% CI 5.1 to 7.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
19	54	56	> 1 year	Mean 12 months: 7.8 (1.3) 24 months: 12.1 (2.8)	NR	8.3	NR	5.2	NR	NR	NR	NR	NR	1 year: 255 μm (50), 2 year: 245 μm (48)	NR	None
20	35	35	2 years	Anti-VEGF-naïve cohort: After study enrolment, patients received mean 8.9 (1.4) injections in the period from baseline to 12 months of TAE. Due to the definition of baseline in this cohort as the start date of ranibizumab injection, these numbers include the monthly ranibizumab loading phase, and thus may be higher than expected for a T&E regimen.	Anti-VEGF-naïve cohort: T&E clinic visits coincided with injection visits	Anti-VEGF-naïve cohort: 7.6 (95%CI: 2.8, 12.4).	Gain: 25.9% Loss: 3.7%	NR	NR	NR	NR	NR	NR	Anti-VEGF-naïve cohort: mean change from baseline CSRT was -68 μm (95%CI: -107, -29).	NR	NR
21	42	42	> 1 year	7 or less IVI group: mean 6.6 over 1 year; 8 IVI group - 8.0 over 1 year	NR	2.6 (95% CI -1.8, 7.0) for 7 or less IVI; 5.9 (95% CI 1.0, 10.8) for 8 IVI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
22	139	148	3 years	Year 1 = 7.2 ± 1.8; Year 2 = 12 ± 3.8; Year 3= 15.9 ± 6.1	NR	5.9 ± 13.8	Gain: 25% Loss: 6.8%	6.4 ± 14.9	Gain: 28.2% Loss: 9.2%	36 months: 6.6 ± 15.4 gain	Gain: 30.5% Loss: 11.1%	Note values relate to >73 logMAR letters Baseline: 10.8% Year 1: 30.4% Year 2: 38.9% Year 3: 28.7%	NR	Year 1 = -71 μm ± 100; Year 2 = -75 μm ± 95; Year 3 = -78 μm ± 101	Year 1 = 67%, Year 2 = 61%; Year 3 = 67%	NR
23	69	72	1 year	7.0 ± 1.4	NR	3.2 ± 13.4	NR	NR	NR	NR	NR	NR	NR	12 months: 307 μm ± 85	NR	NR
24	3357	3357	2 years	First year: 7.7 (95%CI: 7.6-7.8); Over two years: 13.0 (95%CI: 12.8-13.2)	NR	5.5 (95%CI 5.0-6.0)	NR	4.9 (95%CI 4.2-5.6)	NR	NR	NR	Baseline: 24% Year 1: 42% Year 2: 44%	NR	NR	NR	NR
25	86	86	8 years	Median: Year 1: 6; Year 2: 4; Year 3: 4; Year 4: 4; Year 5: 5; Year 6: 4; Year 7: 3; Year 8: 3	NR	6.9 (12.3)	NR	4.1 (14.3)	NR	3rd year: -0.8 (19.2); 4th year: -0.8 (21.0); 5th year: -1.9 (23.0); 6th year: -3.8 (23.3); 7th year: -6.4 (24.8); 8th year: -9.1 (25.0)	At 8 years: 10.5%	Baseline: 33.4% Year 8: 26.3%	NR	Baseline median CRT = 295 μm (IQR 254-349). At 8 years = 209 μm (IQR 182-254)	NR	NR
26	468	512	5 years	For whole cohort: 1st year = 7.8 (SD 1.3), 2nd year = 4.9 (SD 2.7), 3rd year = 3.8 (SD 3.1), 4th year = 3.5 (SD 3.1), 5th year = 3.2 (SD 3.2); For patients who completed 4 years of treatment - 1st year = 7.9 (SD 1.3), 2nd year = 5.2 (SD 2.7), 3rd year = 4.1 (SD 3.1), 4th year = 3.7 (SD 3.2), 5th year = 3.2 (SD 3.2)	NR	Whole cohort 5.6 (SD 15.4) vs completers 6.3 (SD 14.3)	NR	Whole cohort 3.0 (SD 18.3) vs completers 3.9 (SD 18.3)	NR	3rd year: whole cohort 0.3 (SD 20.5) vs completers 1.7 (SD 19.9); 4th year: whole cohort -1.9 (SD 22.7) vs completers -1.2 (SD 22.3); 5th year: whole cohort -2.9 (SD 23.4) vs completers -2.9 (SD23.4)	NR	Baseline: 32.2% Year 1: 54.4% Year 2: 50.3% Year 3: 44.4% Year 4: 42.6% Year 5: 39.9%	NR	NR	NR	NR

Supplementary Table 2. Bias Assessment: Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist.[27]

		Study Objective	Study Design			Study Population		
Reference	Year	Clear Objectives	Prospective	Multi-Centre	Consecutive Recruitment	Patient Characteristics Described	Clear Inclusion / Exclusion Criteria	Similar Point in Disease
Gupta et al.[1]	2011	Yes	No	No	Unclear	Yes	Yes	Yes
Kumar et al.[2]	2011	Yes	Yes	No	Yes	Yes	Yes	Yes
Shona et al.[3]	2011	Yes	No	No	Unclear	Yes	Yes	Yes
Pushpoth et al.[4]	2012	Yes	No	No	Yes	Yes	Yes	Unclear
Muniraju et al.[5]	2013	Yes	No	No	Yes	Partial	Yes	Yes
Tan et al.[6]	2013	Yes	No	No	Unclear	Partial	Yes	Yes
Ross et al.[7]	2013	Yes	Yes	No	Unclear	Yes	Yes	Yes
Chavan et al.[8]	2014	Yes	Yes	No	Yes	Yes	Yes	Yes
UK AMD EMR[9]	2014	Yes	No	Yes	Unclear	Yes	Yes	Yes
Basheer et al.[10]	2015	Yes	Yes	No	Unclear	Partial	Yes	Yes
Borooah et al.[11]	2015	Yes	No	Yes	Unclear	Partial	Yes	Unclear
Williams et al.[12]	2015	Yes	Yes	No	Yes	Partial	Yes	Yes
Buckle et al.[13]	2016	Yes	No	No	Unclear	Yes	Yes	Yes
Razi et al.[14]	2016	Yes	No	No	Yes	Yes	Yes	Yes
Talks et al.[15]	2016	Yes	No	Yes	Unclear	Yes	Yes	Yes
Almuhtaseb et al.[16]	2017a	Yes	No	No	Unclear	Yes	Yes	Yes
Almuhtaseb et al.[17]	2017b	Yes	No	Yes	Unclear	Yes	Yes	Yes
Lee et al.[18]	2017	Yes	No	Yes	Unclear	Yes	Yes	Yes
Vardarinos et al.[19]	2017	Yes	No	No	Unclear	Yes	Yes	Yes
Yang et al.[20]	2017	Yes	Partial	Yes	Unclear	Yes	Yes	Yes
Ozturk et al.[21]	2018	Yes	No	No	Unclear	Yes	Yes	Yes
Eleftheriadou et al.[22]	2018	Yes	No	No	Yes	Yes	Yes	Yes
Fulcher et al.[23]	2019	Yes	No	No	Unclear	Yes	Yes	Yes
Fasler et al.[24]	2019	Yes	No	No	Unclear	Yes	Yes	Yes
Horner et al.[25]	2019	Yes	No	No	Yes	Yes	Yes	Yes
Chandra et al.[26]	2020	Yes	No	No	Yes	Yes	Yes	Yes

		Intervention and co-intervention		Outcome Measures				Statistical Analysis
Reference	**Year**	**Intervention Described Clearly**	**Co-Interventions Described Clearly**	***A priori* outcomes measures**	**Masked Outcome Assessors**	**Appropriate Outcome Measures**	**Before and After Intervention**	**Appropriate Statistical Tests**
Gupta et al.[1]	2011	Yes	Yes	Yes	No	Yes	Yes	Yes
Kumar et al.[2]	2011	Yes	Yes	Yes	No	Yes	Yes	Yes
Shona et al.[3]	2011	Yes	Yes	Yes	No	Yes	Yes	Yes
Pushpoth et al.[4]	2012	Yes	Yes	Yes	No	Yes	Yes	Yes
Muniraju et al.[5]	2013	Yes	Yes	Yes	No	Yes	Yes	Yes
Tan et al.[6]	2013	Yes	Yes	Yes	No	Yes	Yes	Yes
Ross et al.[7]	2013	Yes	Yes	Yes	No	Yes	Yes	Yes
Chavan et al.[8]	2014	Yes	Yes	Yes	No	Yes	Yes	Yes
UK AMD EMR[9]	2014	Yes	Yes	Yes	No	Yes	Yes	Yes
Basheer et al.[10]	2015	Yes	Yes	Yes	No	Yes	Yes	Unclear
Borooah et al.[11]	2015	Yes	Yes	Yes	No	Yes	Yes	Yes
Williams et al.[12]	2015	Yes	Yes	Yes	No	Yes	Yes	Unclear
Buckle et al.[13]	2016	Yes	Yes	Yes	No	Yes	Yes	Yes
Razi et al.[14]	2016	Yes	Yes	Yes	No	Yes	Yes	Unclear
Talks et al.[15]	2016	Yes	Yes	Yes	No	Yes	Yes	Yes
Almuhtaseb et al.[16]	2017	Yes	Yes	Yes	No	Yes	Yes	Yes
Almuhtaseb et al.[17]	2017	Yes	Yes	Yes	No	Yes	Yes	Yes
Lee et al.[18]	2017	Yes	Yes	Yes	No	Yes	Yes	Yes
Vardarinos et al.[19]	2017	Yes	Yes	Yes	No	Yes	Yes	Yes
Yang et al.[20]	2017	Yes	Yes	Yes	No	Yes	Yes	Yes
Ozturk et al.[21]	2018	Yes	Yes	Yes	No	Yes	Yes	Yes
Eleftheriadou et al.[22]	2018	Yes	Yes	Yes	No	Yes	Yes	Yes
Fulcher et al.[23]	2019	Yes	Yes	Yes	No	Yes	Yes	Yes
Fasler et al.[24]	2019	Yes	Yes	Yes	No	Yes	Yes	Yes
Horner et al.[25]	2019	Yes	Yes	Yes	No	Yes	Yes	Yes
Chandra et al.[26]	2020	Yes	Yes	Yes	No	Yes	Yes	Yes

		Results and Conclusions					Competing interests and sources of support	Domains completed
Reference	**Year**	**Follow-up Long Enough**	**Losses to Follow-up Reported**	**Estimates of Random Variability**	**Adverse Events**	**Conclusions Supported by Results**	**Competing Interests Reported**	
Gupta et al.[1]	2011	Yes	Yes	Yes	Partial	Yes	Partial	15.5
Kumar et al.[2]	2011	Yes	Yes	Yes	Partial	Yes	Partial	17
Shona et al.[3]	2011	Yes	Yes	Yes	Partial	Yes	Partial	15.5
Pushpoth et al.[4]	2012	Yes	Yes	Yes	Partial	Yes	Yes	16
Muniraju et al.[5]	2013	Yes	Yes	Yes	No	Yes	Partial	15
Tan et al.[6]	2013	Yes	Yes	Yes	No	Yes	No	14
Ross et al.[7]	2013	Yes	Yes	Yes	Partial	Yes	Partial	16.5
Chavan et al.[8]	2014	Yes	Yes	Yes	No	Yes	Partial	16.5
UK AMD EMR[9]	2014	Yes	Yes	Yes	Partial	Yes	Partial	17
Basheer et al.[10]	2015	Yes	Yes	Partial	No	Yes	Yes	15
Borooah et al.[11]	2015	Yes	Yes	Yes	No	Yes	Yes	15.5
Williams et al.[12]	2015	Yes	Yes	Partial	No	Yes	Partial	15
Buckle et al.[13]	2016	Yes	Yes	Partial	Partial	Yes	Partial	15
Razi et al.[14]	2016	Yes	Yes	Partial	Partial	Yes	Partial	15
Talks et al.[15]	2016	Yes	Yes	Yes	No	Yes	Yes	16.5
Almuhtaseb et al.[16]	2017	Yes	Yes	Partial	No	Yes	Partial	14.5
Almuhtaseb et al.[17]	2017	Yes	Yes	Yes	No	Yes	Yes	16.5
Lee et al.[18]	2017	Yes	Yes	Yes	No	Yes	Yes	16.5
Vardarinos et al.[19]	2017	Yes	Yes	Yes	Yes	Yes	Yes	16.5
Yang et al.[20]	2017	Yes	Yes	Yes	No	Yes	Yes	17
Ozturk et al.[21]	2018	Yes	Yes	Yes	No	Yes	Yes	15.5
Eleftheriadou et al.[22]	2018	Yes	Yes	Yes	No	Yes	Yes	16
Fulcher et al.[23]	2019	Yes	Yes	Yes	No	Yes	Yes	15.5
Fasler et al.[24]	2019	Yes	Yes	Yes	No	Yes	Yes	15.5
Horner et al.[25]	2019	Yes	Yes	Yes	No	Yes	Yes	16
Chandra et al.[26]	2020	Yes	Yes	Yes	Partial	Yes	Yes	16.5

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