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Comparative Effectiveness of Pharmacological Interventions for Nonalcoholic Steatohepatitis: A Systematic Review and Network Meta-analysis

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We performed a Bayesian network meta-analysis combining direct and indirect treatment comparisons to assess the comparative effectiveness of pharmacological agents for the treatment of nonalcoholic steatohepatitis (NASH). Through systematic literature review, we identified nine randomized, controlled trials (RCTs) including 964 patients with biopsy-proven NASH, comparing vitamin E, thiazolidinediones (TZDs), pentoxifylline, or obeticholic acid to one another or placebo. The primary outcome was improvement in fibrosis stage; secondary outcomes were improvement in ballooning degeneration, lobular inflammation, and steatosis. We reported relative risks (RRs) and 95% confidence intervals (CIs) from direct meta-analysis and 95% credible intervals (CrIs) from Bayesian network meta-analysis, and used Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria to appraise quality of evidence. Moderate-quality evidence supports the use of pentoxifylline (RR, 0.26; 95% CrI: 0.05-1.00) and obeticholic acid (RR, 0.81; 95% CI: 0.70-0.95) over placebo in improving fibrosis. High-quality evidence supports the effect of vitamin E, TZDs, and obeticholic acid over placebo in improving ballooning degeneration. All four interventions seemed to have at least moderate-quality evidence over placebo to improve steatosis. Moderate-quality evidence supports that TZDs, pentoxifylline, and obeticholic acid decrease lobular inflammation. All the head-to-head comparisons were supported by very-low-quality evidence except for superiority of TZDs over vitamin E on improving steatosis and lobular inflammation, which had moderate-quality evidence. *Conclusions*: Based on direct and network meta-analysis, pentoxifylline and obeticholic acid improve fibrosis, and vitamin E, TZDs, and obeticholic acid improve ballooning degeneration in patients with NASH. Future comparative trials of combination therapies targeting distinct histological features are warranted. (HEPATOLOGY 2015;62:1417-1432)

Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease worldwide and is associated with increased liver-related mortality and hepatocellular carcinoma.[1] It is currently the second-most common indication for liver transplantation in the United States.[2] The rate of progression of fibrosis in patients with NAFLD is widely variable and depends on several clinical and histological factors, such as age, diabetes, obesity, hypertension, and presence of steatohepatitis; patients with non-alcoholic steatohepatitis (NASH) progress at a faster rate than patients with isolated fatty liver.[3-5]

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CrI, credible interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ITT, intention to treat; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; RCTs, randomized, controlled trials; RR, relative risk; TNF-α, tumor necrosis factor alpha; TZDs, thiazolidinediones; UCDA, ursodeoxycholic acid.

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The mainstay of management of NASH is lifestyle intervention, including diet, behavioral modification, and physical activity, directed toward weight loss.[6] Multiple pharmacological agents have been studied, with variable efficacy.[7] Evidence from clinical trials suggests that vitamin E, thiazolidinediones (TZDs), pentoxifylline, or obeticholic acid (OCA) improve histological features in NASH, but improvement in individual features of fibrosis and inflammation varies among therapeutic agents. TZDs improve inflammation and steatosis, but not fibrosis, in patients with NASH[8]; vitamin E is reported to have a similar response,[9] whereas pentoxifylline[10] may improve fibrosis and inflammation. Recently, the farnesoid X nuclear receptor ligand, OCA, has also been shown to decrease NAFLD activity score in noncirrhotic NASH.[11] However, most of these randomized, controlled trials (RCTs) are small and placebo controlled, with a paucity of trials comparing different pharmacological interventions, precluding assessment of the comparative effectiveness of these interventions. Direct meta-analyses provide only partial information in this case, because they can only answer questions about pairs of treatments and hence do not optimally inform decision making on comparative effectiveness of agents.

Network meta-analysis can help assess comparative effectiveness of multiple interventions and synthesize evidence across a network of RCTs.[12,13] This method involves the simultaneous analysis of direct evidence (from RCTs directly comparing treatments of interest) and indirect evidence (from RCTs comparing treatments of interest with a common comparator, such as placebo) to calculate a mixed-effect estimate as the weighted average of the two.[14] Such a technique may improve the precision of the estimate (compared with direct evidence alone) and also allows estimation of the comparative efficacy of two active treatments, even if no studies directly compare them.[15] For example, through a Bayesian network of three agents, A, B, and C, if we know the relationship between A and B, and B and C, we can infer probabilistic relationship between A and C.[12,13]

Presence of hepatic fibrosis is one of the key predictors for the future risk of progression to cirrhosis and liver-related mortality. In a recent prospective cohort study of 619 patients with biopsy-confirmed NAFLD followed over 12.6 years, Angulo et al. observed that baseline fibrosis stage was the only histological variable associated with liver-related events during follow-up.[16] Individual RCTs conducted in NASH have not been powered to detect improvement in fibrosis. Owing to the emergence of several therapies with an antifibrotic mechanism of action, a pooled comparative effectiveness assessment of current therapies in NASH is quintessential to (1) show whether certain therapies may improve fibrosis and (2) understand the quantitative effect sizes by a network meta-analysis, which would help design appropriately powered trials with improvement in hepatic fibrosis as the primary outcome.

Therefore, we performed a systematic review with a direct meta-analysis and Bayesian network meta-analysis combining direct and indirect evidence to compare the relative efficacy of all pharmacological interventions (vitamin E, TZDs, pentoxifylline, or OCA) for the management of NASH, using improvement in fibrosis as the primary endpoint. We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for network meta-analysis to appraise quality of evidence.[17]

Materials and Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and was conducted following an *a priori* established protocol.[18,19] We also followed good research practices as outlined in the International Society for Pharmacoeconomics and Outcomes Research report on interpreting indirect treatment comparisons and network meta-analysis for health care decision making.[20]

Selection Criteria. Studies included in this meta-analysis were RCTs that met the following inclusion criteria: (1) Patients with biopsy-proven NASH; (2) intervention: established or potentially beneficial therapies for NAFLD including vitamin E, TZDs, pentoxifylline, or OCA or a combination of these for at least 1 year, based on American Association for the Study of Liver Diseases (AASLD) guidelines; (3) comparator: another active agent, or placebo; and (4) primary

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outcome: improvement in fibrosis; secondary outcomes included ballooning degeneration, steatosis, and/or lobular inflammation.

We excluded (1) observational studies, (2) trials of lifestyle interventions, including diet, weight loss, and exercise (nonstandardized cointerventions in RCTs of pharmacological agents), (3) trials with short period of follow-up (<6-month), and (4) trials of futile therapy (e.g., metformin, statins, omega-3 fatty acids, ursodeoxycholic acid [UDCA], and so on), based on AASLD guidelines.[6]

Search Strategy. The search strategy was designed and conducted by an experienced medical librarian with input from study investigators, utilizing several databases with variant controlled vocabularies, expanded terminology, varying algorithms, and keyword capabilities for RCTs of pharmacological therapy for NAFLD. We searched multiple electronic databases (Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus) from inception through November 30, 2014. Two study investigators (S.S., R.K.) independently reviewed the titles and abstracts of studies identified in the search, to exclude studies that did not address the research question of interest, based on prespecified inclusion and exclusion criteria. The full text of the remaining articles was evaluated to assess relevance. Conflicts in study selection at this stage were resolved by consensus, referring back to the original article in consultation with the principal investigator (R.L.). We also performed a recursive search of the bibliographies of these selected articles as well as published systematic reviews on this topic, to identify any additional studies. Finally, we conducted a manual search of abstracts from major gastroenterology conferences (Digestive Disease Week, the Liver Meeting organized by AASLD, and the International Liver Meeting organized by the European Association for the Study of the Liver) from 2010 to 2014 to identify additional abstracts on the topic. Supporting Fig. 1 shows the schematic diagram of study selection.

Data Abstraction and Quality Assessment. Data on the following study-, patient-, and treatment-related characteristics were abstracted onto a standardized form, by two authors independently: (1) study characteristics: primary author, time period of study/year of publication, geographical location and centers where study was conducted, and duration of follow-up; (2) patient characteristics: age, sex, body mass index (BMI), diabetes; (3) NAFLD characteristics: NAFLD Activity Score (NAS) with fibrosis and ballooning degeneration subscores, alanine aminotransferase/aspartate aminotransferase (ALT/AST), and presence of NASH at baseline in treatment groups; (4) treatment characteristics: dosing and schedule of intervention and concomitant nonpharmacological interventions (diet, exercise, and so on); (5) outcome assessment: scoring system used for histological classification of NAFLD, number of patients in intervention and comparator group, and proportion achieving the outcomes of interest (as dichotomous variable), change in liver aminotransferases (ALT and AST), weight and low-density lipoprotein (LDL) cholesterol from baseline in each treatment group; and (6) adverse effects: proportion of patients with serious adverse events (AEs).

The risk of bias of individual studies was assessed in the context of the primary outcome, using the Cochrane Risk of Bias assessment tool.[21] Using this tool, studies were deemed to be at high, low, or unclear risk of bias based on adequacy of sequence generation, allocation concealment, blinding, method of addressing incomplete data, selective reporting, and other biases.

Outcomes Assessed. The primary outcome was proportion of patients with improvement in fibrosis. Secondary outcomes were proportion of patients with improvement in ballooning degeneration, steatosis, and/or lobular inflammation. We were unable to assess NAS as an outcome given its limited reporting in trials. If outcomes were reported at multiple time points, we examined results reported at 12 months. The denominator was based on a modified intention-to-treat (ITT) analysis, whereby only patients who received at least one dose of the medication were included; patients without follow-up biopsy (or with lack of information on follow-up histological findings) were deemed treatment failures.

Statistical Analysis. Direct meta-analysis was performed using a random-effects model to estimate pooled relative risk (RR) and 95% confidence intervals (CIs) incorporating within- and between-study heterogeneity.[22] We assessed statistical heterogeneity using the I^2 statistic, with values over 50% indicating substantial heterogeneity,[23] and evaluated for publication bias by examining funnel plot asymmetry and Egger's regression test.[24] Direct comparisons were performed using RevMan software (v5.3; Cochrane Collaboration, Copenhagen, Denmark).[25]

To incorporate indirect comparisons, we conducted random-effects Bayesian network meta-analyses using Markov chain Monte Carlo methods in WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK), following methods described by Lu and Ades.[14,26] We modeled the comparative efficacy of any two treatments as a function of each treatment relative to the reference

treatment (i.e., placebo). This approach assumes "consistency" of treatment effects across all included trials—that is, the direct and indirect estimates are the same effects. Network consistency was evaluated by comparing the direct estimates to the indirect estimates. Indirect effects were estimated using a node splitting technique. We estimated the posterior distribution of all parameters using noninformative priors to limit inference to data derived from the trials at hand (i.e., we made no assumptions about the efficacy of these drugs from data external to the trials included in this systematic review). We updated the Markov chain Monte Carlo model with 100,000 simulated draws after a burn-in of 1,000 iterations. The median of the posterior distribution based on 100,000 simulations was reported as the point estimate (RR), and the corresponding 95% credible intervals (CrIs, or Bayesian CI) was obtained using the 2.5th and 97.5th percentiles of the posterior distribution, after adjusting for multiple arm trials (model available upon request).

We assessed the probability that each intervention was the most efficacious in improving fibrosis or ballooning degeneration, the second best, the third best, and so on, by calculating the RR for each drug compared with an arbitrary common control group, and counting the proportion of iterations of the Markov chain in which each drug had the highest RR, the second highest, and so on.

Quality of Evidence. We followed the GRADE approach to rate the quality of evidence of estimates derived from network meta-analysis.[17,27] In this approach, direct evidence from RCTs starts at high quality and can be rated down, based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity), and/or publication bias, to levels of moderate, low, and very low quality. The rating of indirect estimates starts at the lowest rating of the two pair-wise estimates that contribute as first-order loops to the indirect estimate, but can be rated down further for imprecision or intransitivity (dissimilarity between studies in terms of clinical or methodological characteristics). If direct and indirect estimates are similar (i.e., coherent), then the higher of their rating can be assigned to the network meta-analysis estimates. When the direct evidence had higher quality, we used that over the network evidence.

Results

From a total of 315 unique studies identified using the search strategy, we included nine RCTs in this network meta-analysis.[9-11,28-33] Two trials, one each for vitamin E and rosiglitazone, were excluded because of comparison with nonstandardized interventions (silybin+phosphatdylcholine vs. vitamin E; and rosiglitazone vs. rosiglitazone+metformin vs. rosiglitazone+losartan).[34,35] Three trials (of vitamin E, rosiglitazone, and pentoxifylline) were excluded because the comparator group received nonstandardized dietary intervention.[36-38] Six trials were excluded because of lack of histological endpoints (three trials of vitamin E,[39-41] two of pioglitazone,[42,43] and one of OCA).[44] Three trials (one each of vitamin E, pioglitazone, and vitamin E+pioglitazone) were excluded because a proportion of patients with improvement in fibrosis was not reported.[45-47] Figure 1 demonstrates the available direct comparisons and network of trials.

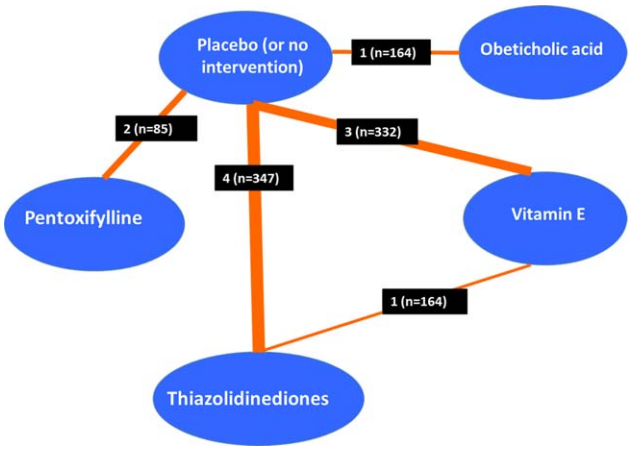

Fig. 1. Network of included studies with the available direct comparisons.

Characteristics and Quality of Included Studies. Table 1 summarizes the RCTs included in the network meta-analysis. Overall, these nine trials had 964 participants with NASH.[9-11,28-33] Seven of these were two-arm trials,[10,11,28,30-33] comparing active agent with placebo; one RCT (PIVENS) was a three-arm trial comparing vitamin E, pioglitazone, and placebo.[9] One trial of pediatric patients with NAFLD (42.2% with NASH) compared vitamin E with placebo and metformin, but we only included a comparison of vitamin E and placebo for our analysis.[29]

Three RCTs (332 patients) compared vitamin E with placebo and reported changes in fibrosis as endpoint.[9,28,29] Four RCTs (347 patients) compared TZDs (3 pioglitazone,[9,31,32] one rosiglitazone[33]) to placebo or vitamin E. Two small RCTs (85 patients) compared pentoxifylline to placebo,[10,30] and one RCT (164 patients) compared OCA to placebo.[11]

Supporting Table 2 describes the baseline characteristics of patients included in these trials. The mean age of participants in the active intervention arms of RCTs in adults with NASH ranged from 45 to 53 years; 30%-69% were males. Two RCTs included only nondiabetic

Table 1. Characteristics of Included RCTs Comparing Different Pharmacological Interventions for NASH (Arranged Chronologically, by Intervention Groups)

First Author, Year (Trial Name)	Study Design	Study Location, Period	Follow-up Duration	Intervention N = ITT	Control N = ITT	Concomitant Therapies		Main Results (Histological Outcomes)
						Diet/Exercise	Medications	
Vitamin E vs. placebo								
Harrison, 2003	SC, DB, PC	USA, 2000-2002	6 months	Vitamin E (1000 IU/d) + Vitamin C (1,000 mg/d), N = 25	Placebo, N = 24	NHLBI 1,600 cal and written exercise plan	None specified	1. Vitamin E+C was superior to placebo in improving fibrosis score. 2. There was no significant difference between vitamin E+C and placebo in improving inflammation/necrosis score.
Sanyal, 2010 (PIVENS)	MC, DB, PC	USA, 2005-2007	96 weeks	Vitamin E 800 IU/d, N = 84	Placebo, N = 83	Standardized diet and exercise (details NA)	No medication known to induce NASH, others not specified	1. Vitamin E (43%), but not pioglitazone (34%), was superior to placebo (19%) for improving NASH (improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the NAS to a score of 3 or less or a decrease in the activity score of at least 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score). 2. Pioglitazone (47%), but not vitamin E (36%), was superior to placebo (21%) in inducing resolution of NASH.
Lavine, 2011 (TONIC)	MC, DB, PC	USA, 2005-2010	96 weeks	Vitamin E 800 IU/d, N = 58 (metformin-alone arm was not considered in analysis)	Placebo, N = 58	Standardized diet and exercise (details NA)	Not on glucocorticoids, tetracyclines, anabolic steroids, valproic acid	1. Vitamin E (mean change in NAS from baseline, −1.8), but not metformin (−1.1), was superior to placebo (−0.7) in improving NAS. 2. Vitamin E (58%), but not metformin (41%), was superior to placebo (28%) in inducing resolution of NASH.
Pentoxifylline vs. placebo								
Van Wagner, 2011	SC, DB, PC	USA, 2005-2008	1 year	Pentoxifylline 400 mg TID, N = 21	Placebo, N = 9	No specific dietary or exercise instructions	Not on thiazolidinediones, metformin, vitamin E, anti-TNF-α agent, theophylline; =>insulin or sulfonylurea OK if stable for 6 months	1. Pentoxifylline (mean change in NAFLD activity score from baseline, −1.4) was superior to placebo (−0.4) for improving NAS. 2. Pentoxifylline (44%) was not superior to placebo (28%) in inducing resolution of NASH.

Table 1. *Continued*

First Author, Year (Trial Name)	Study Design	Study Location, Period	Follow-up Duration	Intervention N = ITT	Control N = ITT	Concomitant Therapies		Main Results (Histological Outcomes)
						Diet/Exercise	Medications	
Zein, 2011	MC, DB, PC	USA, 2006-2009	1 year	Pentoxifylline 400 mg TID, N = 26	Placebo, N = 29	Individualized nutritional counseling	No insulin therapy, Vitamin E, TZDs, α-glucusidase inhibitors, coumadin	1. Pentoxifylline (38.5%) was superior to placebo (13.8%) in inducing a 2-point decrease in NAS. 2. Pentoxifylline (25%) was superior to placebo (3.9%) in inducing resolution of NASH.
Thiazolidinediones vs. placebo								
Belfort, 2006	MC, DB, PC	USA, 2002-2004	6 months	Pioglitazone 45 mg/d, N = 26	Placebo, N = 21	Hypocaloric diet (500 kcal less)	Not on insulin, metformin, or other TZDs	1. Pioglitazone, but not placebo, was associated with improvement in fibrosis score. 2. Pioglitazone (85%) was superior to placebo (38%) in improving necroinflammation.
Ratziu, 2008 (FLIRT)	SC, DB, PC	France, 2003-2004	1 year	Rosiglitazone 4 mg/d for 1 month, then 8 mg/d, N = 32	Placebo, N = 31	Healthy eating and twice-weekly exercise (details NA)	Not on insulin, UDCA, or medication that induces NASH (not specified)	1. There was no significant difference between rosiglitazone (mean change in NAS from baseline, −1.0) and placebo (0.0) in improving NAS. 2. Rosiglitazone was superior to placebo in improving steatosis, but not fibrosis, hepatocyte ballooning and lobular inflammation.
Aithal, 2008	MC, DB, PC	UK, 2002-2006	1 year	Pioglitazone 30 mg/d, N = 37	Placebo, N = 37	Hypocaloric diet (500 kcal less), 5×/week exercise	Not on methotrexate, amiodarone, tamoxifen, valproate	1. Pioglitazone (29%) was superior to placebo (20%) in improving fibrosis. 2. Pioglitazone was superior to placebo in improving hepatocellular injury, but comparable in improving steatosis, lobular, and portal inflammation.
Sanyal, 2010 (PIVENS)	MC, DB, PC	USA, 2005-2007	96 weeks	Pioglitazone 30 mg/d, N = 80	Placebo, N = 83	Standardized diet and exercise (details NA)	No medication known to induce NASH, others not specified	1. Vitamin E (43%), but not pioglitazone (34%), was superior to placebo (19%) for improving in NASH (improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the NAS to a score of 3 or less or a decrease in the activity score of at least 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score).

Table 1. *Continued*

First Author, Year (Trial Name)	Study Design	Study Location, Period	Follow-up Duration	Intervention N = ITT	Control N = ITT	Concomitant Therapies		Main Results (Histological Outcomes)
						Diet/Exercise	Medications	
								2. Pioglitazone (47%), but not vitamin E (36%), was superior to placebo (21%) in inducing resolution of NASH.
OCA vs. placebo								
Tetri, 2014 (FLINT)	MC, DB, PC	USA, 2011-2012	72 weeks	Obeticholic acid 25 mg/d, N = 141	Placebo, N = 142	Patient-specific diet, exercise, hyperlipidemia and DM management, no standardized intervention	Use of drugs associated with NAFLD for >2 weeks in the year before randomization	1. OCA (mean change in NAS from baseline, −1.7) was superior to placebo (−0.7) for improving NAFLD activity score. 2. OCA (22%) was not superior to placebo (13%) in inducing resolution of NASH.

Abbreviations: cal, calories; DB, double blinded; DM, diabetes mellitus; IU/d, international units per day; kcal, kilocalories; mg/d, milligrams per day; MC, multicenter; NA, not available; NHLBI, National Heart, Lung, and Blood Institute; OL, open label; PC, placebo controlled; SB, single blinded; SC, single center; USA, United States of America; UK, United Kingdom.

patients[9,31]; 4%-10% of participants in RCTs of pentoxifylline were diabetic, and 53% of patients in the OCA treatment trial were diabetic. One RCT of pioglitazone only included patients with diabetes or impaired glucose tolerance.[32] The mean NAFLD activity score at baseline ranged from 3.1 to 5.7.

Quality assessment was performed in the context of the coprimary outcomes, and overall, the studies were felt to be at low risk of bias, with regard to selection, performance, detection, and reporting bias; two studies did not report method of sequence generation.[30,33] Overall and study-level quality assessments are summarized in Supporting Fig. 2A,B, respectively.

Improvement in Fibrosis

Direct Meta-analysis. Compared to placebo, pentoxifylline (two RCTs; RR, 0.80; 95% CI: 0.65-0.98) and OCA (one RCT; RR, 0.81; 95% CI: 0.70-0.95) were associated with improvement in fibrosis in patients with NASH. In contrast, vitamin E and TZDs were not associated with a significant improvement in fibrosis (Fig. 2A). In the only head-to-head trial, pioglitazone was comparable to vitamin E (RR, 0.93; 95% CI: 0.64-1.32).[9]

Network Meta-analysis. On Bayesian network meta-analysis, as compared to placebo, pentoxifylline was associated with improvement in fibrosis (RR, 0.26; 95% CrI: 0.05-1.00). None of the other interventions, including vitamin E, TZDs, and OCA, were superior to placebo (Table 2). On comparative effectiveness network meta-analysis of active interventions, no agent was clearly superior to others.

Pentoxifylline and OCA had the highest probability of being ranked first and second for improving fibrosis, respectively, whereas TZDs had highest probability of being ranked third (Fig. 3A).

Improvement in Ballooning Degeneration

Direct Meta-analysis. Compared to placebo, vitamin E (two RCTs; RR, 0.73; 95% CI: 0.61-0.86), TZDs (four RCTs; RR, 0.81; 95% CI: 0.71-0.93), and OCA (one RCT; RR, 0.75; 95% CI: 0.65-0.96), but not pentoxifylline (two RCTs; RR, 0.78; 95% CI: 0.48-1.27), were associated with improvement in ballooning degeneration in patients with NASH (Fig. 2B). In the only head-to-head trial, pioglitazone was comparable to vitamin E (RR, 1.14; 95% CI: 0.82-1.59).[9]

Network Meta-analysis. On Bayesian network meta-analysis, as compared to placebo, only TZDs were associated with improvement in ballooning degeneration (RR, 0.43; 95% CrI: 0.17-0.97). None of the other interventions were superior to placebo, though a strong

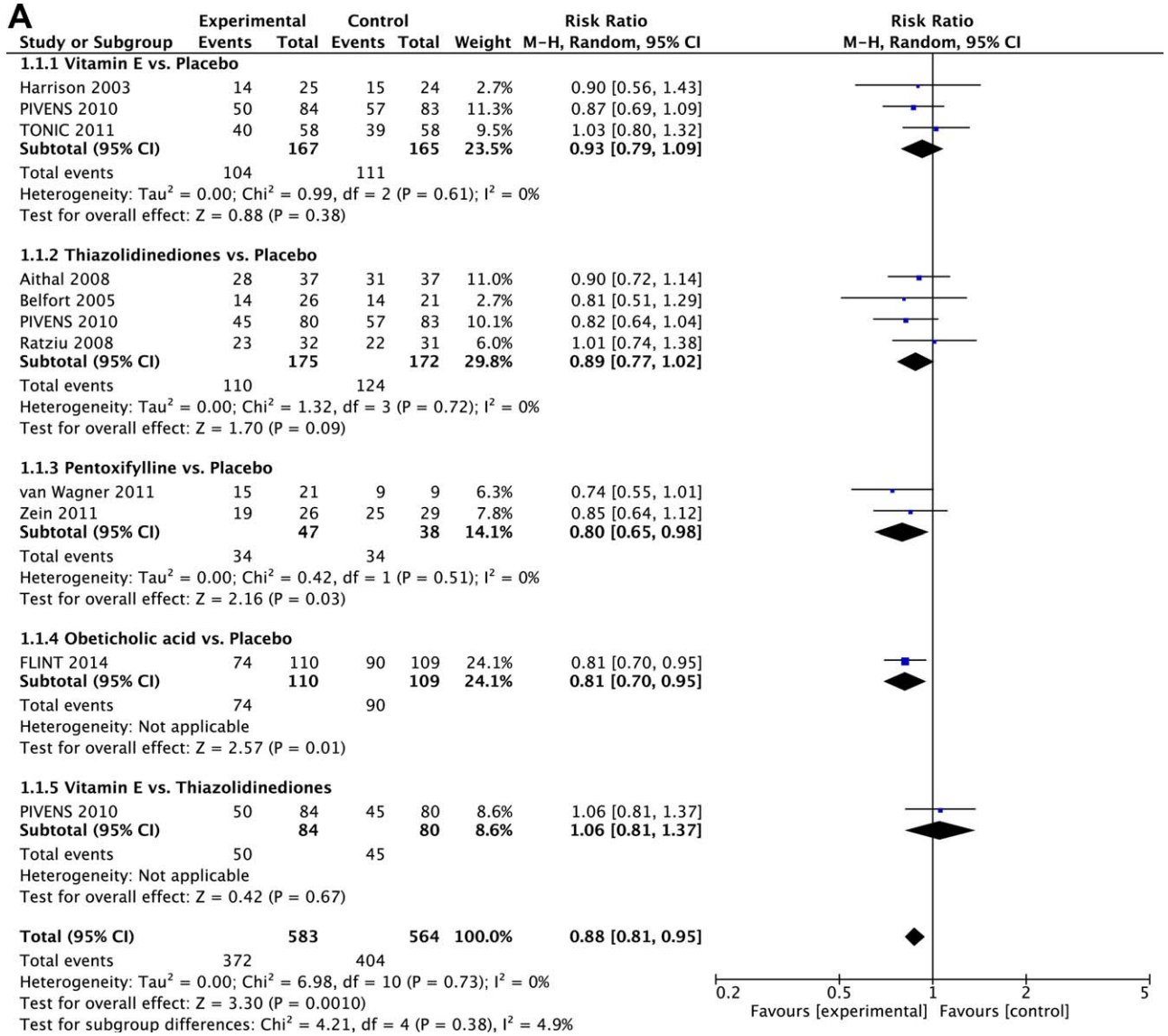

Fig. 2. Direct meta-analysis of different pharmacological interventions for improving (A) fibrosis, (B) ballooning degeneration, (C) steatosis, and (D) lobular inflammation in patients with NASH. Please note that in the forest plot, experimental refers to first treatment group, whereas control refers to the second treatment group. Events refers to failure to achieve outcome of interest (i.e., improvement in fibrosis, ballooning degeneration, steatosis or lobular inflammation). Relative risk <1 indicates superiority of first intervention over second intervention.

trend toward significance was observed with vitamin E (RR, 0.36; 95% CrI: 0.12-1.02; Table 2). On comparative effectiveness network meta-analysis of active interventions, no agent was clearly superior to others, with high degree of imprecision.

Vitamin E had the highest probability of being ranked first- or second-best intervention for improving ballooning degeneration, whereas TZDs had highest probabilities of being ranked second or third (Fig.3B).

Improvement in Steatosis and Lobular Inflammation

Direct Meta-analysis. Compared to placebo, pentoxifylline, TZDs, and OCA improved both steatosis (Fig. 2C) and lobular inflammation (Fig. 2D); vitamin E was associated only with improvement in steatosis without a significant improvement in lobular inflammation. In the only head-to-head trial, pioglitazone was marginally superior to vitamin E for improvement in steatosis and lobular inflammation (RR, 0.78; 95% CI: 0.61-1.00).[9]

Network Meta-analysis. On Bayesian network meta-analysis, as compared to placebo, pentoxifylline and TZDs were associated with significant improvement in steatosis and lobular inflammation (Table 2). On comparative effectiveness network meta-analysis of active interventions, no agent was clearly superior to others, with high degree of imprecision.

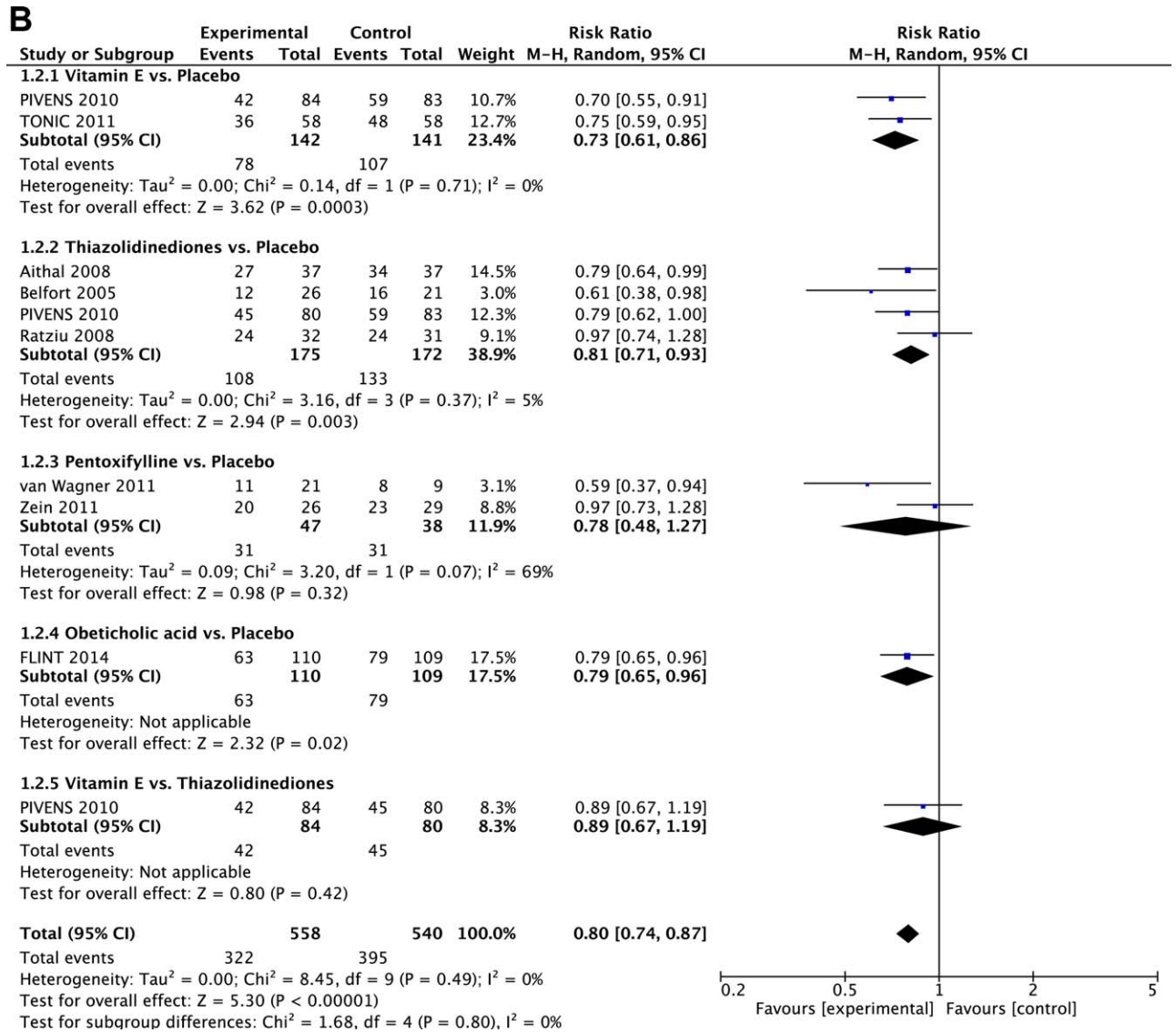

Fig. 2. Continued

Other Outcomes and AEs

Supporting Table 3 reports the change in body mass index (BMI) and biochemical parameters (ALT, LDL, and high-density cholesterol with each agent in each trial. Pentoxifylline and OCA were associated with a decline in BMI, whereas TZD use was associated with a 2%-5% increase in BMI; vitamin E did not significantly modify BMI. All interventions (and the corresponding control group) were associated with a decline in ALT. Whereas most interventions decreased (or did not significantly change LDL), OCA was associated with an increase in LDL and decrease in high-density lipoprotein, without any significant increase in cardiovascular events.

Rate of treatment-related serious AEs was low and comparable to placebo with all active interventions (Supporting Table 4). The observed frequency was 0% (0 of 47) for pentoxifylline (vs. placebo; 0 of 38), 4.9% (7 of 142) for vitamin E (vs. placebo; 10 of 141), 5.7% (10 of 175) for TZDs (vs. placebo; 18 of 172), and 27.3% (30 of 110) for OCA (vs. placebo; 19.3%).

Sensitivity Analysis

Overall, results from prespecified sensitivity analyses after excluding TONIC (pediatric NAFLD study) and trial of rosiglitazone (restricted use) were similar to the primary analysis, albeit with lower precision (Supporting Table 5).

Publication Bias and Network Coherence

We did not find evidence of publication bias (Egger's regression test >0.05 for all comparisons), although the number of studies included in each comparison was very small, thereby making the available methods for evaluating

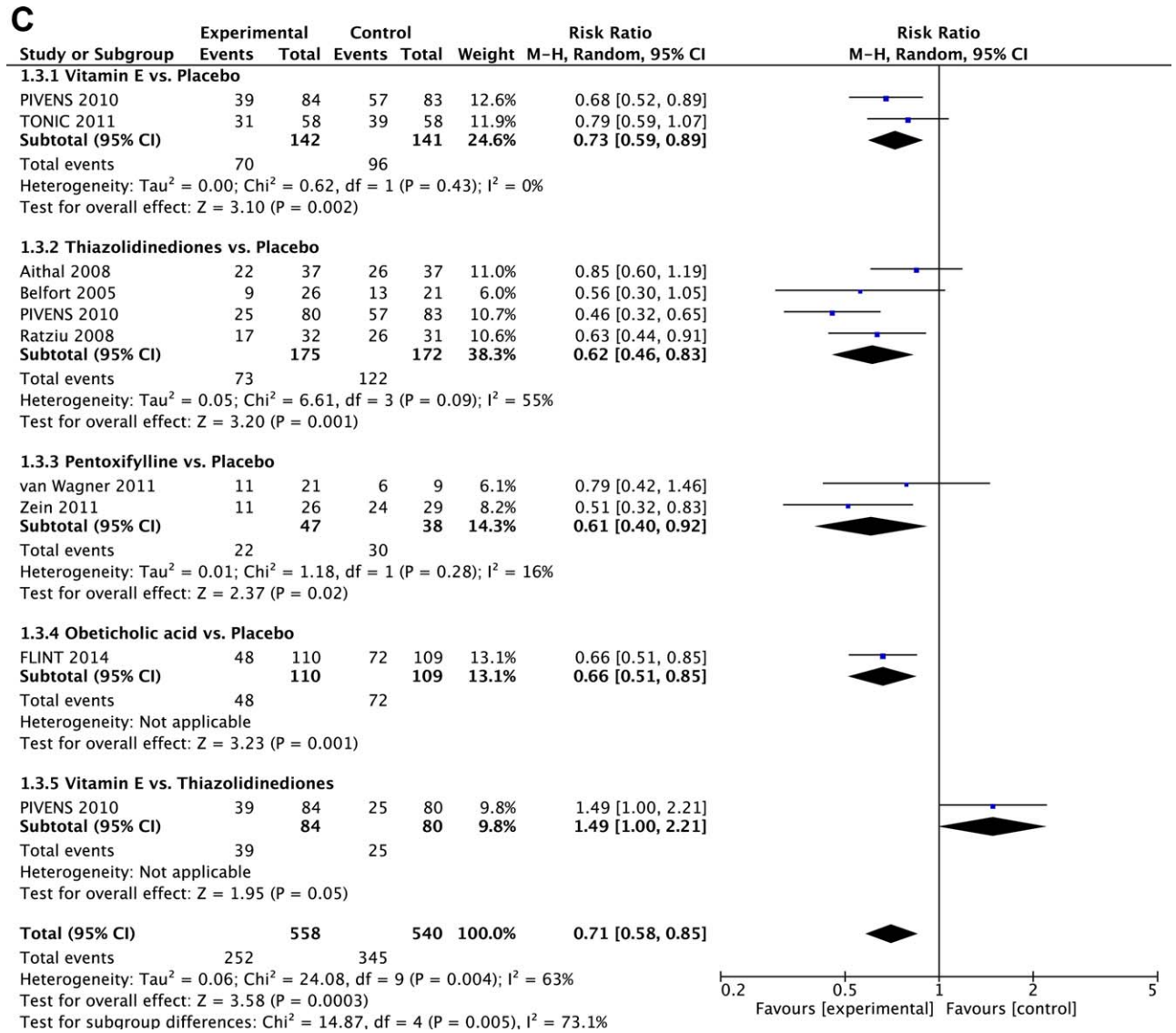

Fig. 2. Continued

publication bias somewhat unreliable. There were no significant differences (incoherence) between direct and indirect estimates where both were available (only for the comparison of TZDs vs. vitamin E), and the two methods had overlapping CIs for all interventions.

Quality of Evidence

The quality of indirect evidence (with no head-to-head trials) was, in general, very low owing to severe imprecision. We did not rate down any comparison for the risk of bias, publication bias, or indirectness, although it is plausible to rate down histological findings on biopsy for indirectness (as surrogate outcomes).

For the outcome of fibrosis and compared to placebo, the effect of pentoxifylline and OCA was supported by moderate-quality evidence (reduced owing to imprecision caused by low number of events). For the outcome of ballooning degeneration and compared to placebo, the effect of vitamin E, TZDs, and OCA was supported by high-quality evidence. For the outcome of steatosis and compared to placebo, all four interventions seemed to have supported at least moderate-quality evidence. For the outcome of lobular inflammation and compared to placebo, pentoxifylline, OCA, and TZDs were supported by moderate-quality evidence. All the head-to-head comparisons were supported by very low quality of evidence except for, probably, superiority of TZDs over vitamin E on steatosis and lobular inflammation, which had moderate-quality evidence. Supplementary Table 6 details the GRADE quality of evidence for direct and network meta-analysis for the outcomes of fibrosis and ballooning degeneration.

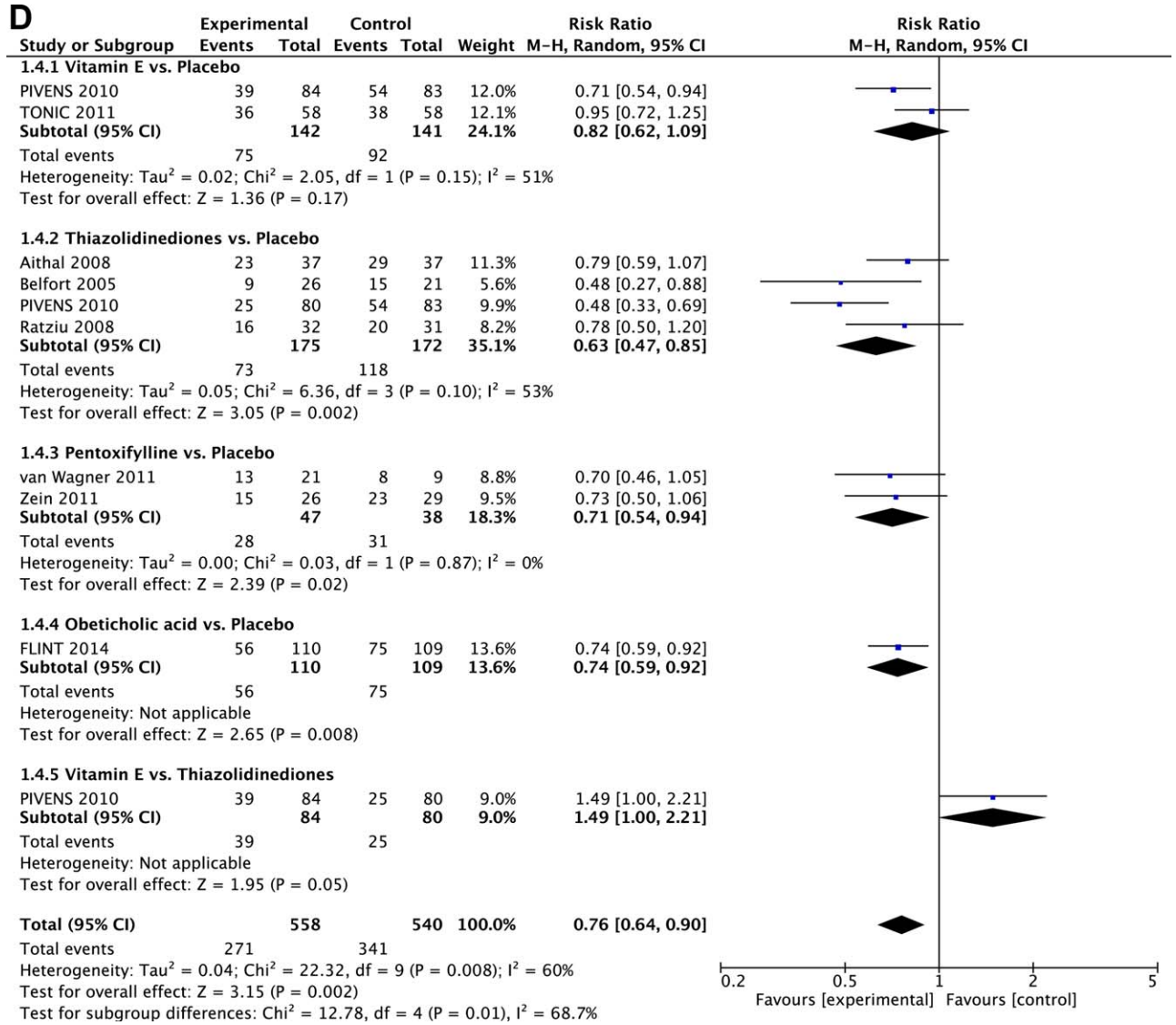

Fig. 2. Continued

Discussion

In this updated systematic review and network meta-analysis, we combined direct and indirect evidence from nine RCTs involving 964 patients with NASH to estimate the relative efficacy of all pharmacological interventions for important histological outcomes, including improvement in fibrosis and ballooning degeneration. We made several key observations: (1) Pentoxifylline and OCA are superior to placebo for improving fibrosis, with moderate confidence in estimates; (2) vitamin E, TZDs, and OCA are superior to placebo for improving ballooning degeneration, with high confidence in estimates; and (3) TZDs, pentoxifylline, and OCA are superior to placebo for improving steatosis and lobular inflammation, with at least moderate confidence in estimates. There is a paucity of comparative effectiveness studies, and new evidence from our analysis supports future RCTs focusing on a combination of pharmacological agents targeting distinct histological features for NASH treatment. Moreover, whereas direct evidence suggests superiority of OCA over placebo for improving NASH histology (fibrosis, ballooning degeneration, steatosis, and lobular inflammation), these findings are based on a single trial, and additional studies are warranted. Since the last published comprehensive systematic review on all treatments for NAFLD in 2010, several new trials have been added; moreover, the previous analysis only included pair-wise direct meta-analysis with limited information on comparative effectiveness of agents for improving objective histological endpoints and did not objectively appraise the overall quality of evidence using the standardized GRADE methodology.[48]

Table 2. Pooled RR of Improvement in Fibrosis, Ballooning Degeneration, Steatosis, and Lobular Inflammation Derived From Direct and Network Meta-analysis With Different Pharmacological Interventions in Patients After NASH

	Fibrosis		Ballooning Degeneration		Steatosis		Lobular Inflammation	
Pharmacological Intervention	**Direct**	**Network**	**Direct**	**Network**	**Direct**	**Network**	**Direct**	**Network**
Compared to placebo								
Pentoxifylline	**0.80 (0.65-0.98)**	**0.26 (0.05-1.00)**	0.78 (0.48-1.27)	0.45 (0.09-1.78)	**0.61 (0.40-0.92)**	**0.23 (0.06-0.86)**	**0.71 (0.54-0.94)**	**0.29 (0.07-0.99)**
Vitamin E	0.93 (0.79-1.09)	0.81 (0.43-1.58)	**0.73 (0.61-0.86)**	0.36 (0.12-1.02)	**0.73 (0.59-0.89)**	0.49 (0.20-1.26)	0.82 (0.62-1.09)	0.64 (0.28-1.55)
TZDs	0.89 (0.77-1.02)	0.68 (0.37-1.26)	**0.81 (0.71-0.93)**	**0.43 (0.17-0.97)**	**0.62 (0.46-0.83)**	**0.29 (0.14-0.62)**	**0.63 (0.47-0.85)**	**0.33 (0.17-0.67)**
OCA	**0.81 (0.70-0.95)**	0.43 (0.15-1.24)	**0.75 (0.65-0.96)**	0.51 (0.11-2.37)	**0.66 (0.51-0.85)**	0.39 (0.11-1.46)	**0.74 (0.59-0.92)**	0.46 (0.14-1.59)
Compared to pentoxifylline								
Vitamin E	–	3.16 (0.71-18.67)	–	0.79 (0.14-5.45)	–	2.13 (0.43-10.32)	–	2.25 (0.51-12.30)
TZDs	–	2.62 (0.58-15.13)	–	0.96 (0.19-5.84)	–	1.26 (0.28-5.61)	–	1.16 (0.29-5.89)
OCA	–	1.65 (0.32-11.87)	–	1.11 (0.16-10.77)	–	1.71 (0.26-10.45)	–	1.63 (0.30-11.08)
Compared to vitamin E								
TZDs	0.93 (0.64-1.32)	0.83 (0.38-1.80)	1.14 (0.82-1.59)	1.21 (0.36-3.86)	**0.78 (0.61-1.00)**	0.59 (0.21-1.69)	**0.78 (0.61-1.00)**	0.52 (0.20-1.35)
OCA	–	0.53 (0.15-1.80)	–	1.41 (0.23-9.42)	–	0.80 (0.16-3.85)	–	0.72 (0.16-3.20)
Compared to TZDs								
OCA	–	0.63 (0.19-2.13)	–	1.17 (0.22-7.24)	–	1.36 (0.29-5.91)	–	1.40 (0.34-5.72)

Column treatment is compared with the row treatment (i.e., row treatment is reference for each comparison). Numbers in parentheses indicate 95% confidence interval for direct meta-analysis and 95% credible interval for network meta-analysis. Results in bold were statistically significant.

Current AASLD guidelines recommend the use of vitamin E and consider the use of pioglitazone in nondiabetic adults with biopsy-proven NASH.[6] There is no recommendation regarding the use of pentoxifylline. Our network meta-analysis suggests that pentoxifylline results in improvement in fibrosis in patients with NASH. There have been several proposed mechanisms by which pentoxifylline may be beneficial in patients with NASH. It inhibits multiple proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), and has antioxidant effects by decreasing production of free oxygen radicals and increasing hepatic glutathione synthesis.[49-51] *In vitro* studies also suggest an antifibrogenic role for pentoxifylline on activated hepatic stellate cells//HSCs by extracellular collagen degradation and reducing key fibrogenic cytokines.[52,53] Pentoxifylline has also been shown to be effective as an antifibrotic agent for radiation-induced fibrosis.[54] However, the evidence supporting the use of pentoxifylline was moderate in quality, limited by the small number of patients included in the two trials of pentoxifylline; future, larger studies are warranted to validate these results.

The strengths of our analyses include the comprehensive and simultaneous assessment of the relative efficacy of all pharmacological agents for management of NASH. Given limited comparative effectiveness studies, it remains difficult for patients and physicians to make informed decisions about which medications are most effective for treating NASH. Direct pair-wise meta-analyses are only partially informative and do not provide information on relative efficacy. In our network meta-analysis, summary estimates from direct and indirect evidence were similar (not incoherent), increasing confidence in findings. We focused on fibrosis as the key clinically relevant histological outcome, which has been associated with increased risk of liver-related events in patients with NAFLD and may serve as important surrogate marker of progression of NASH.[55] We also used GRADE methodology to assess the quality of evidence for this network meta-analysis, which allows direct applicability towards guideline development.

However, there are certain limitations, related to both the network analysis as well as individual studies, which merit further discussion. First, there was a paucity of direct comparative effectiveness studies, and hence the evidence pertaining to relative efficacy of active interventions is of low to very low quality. Second, network meta-analyses may be prone to misinterpretation. The biggest threat to validity of a network meta-analysis is conceptual heterogeneity, wherein there

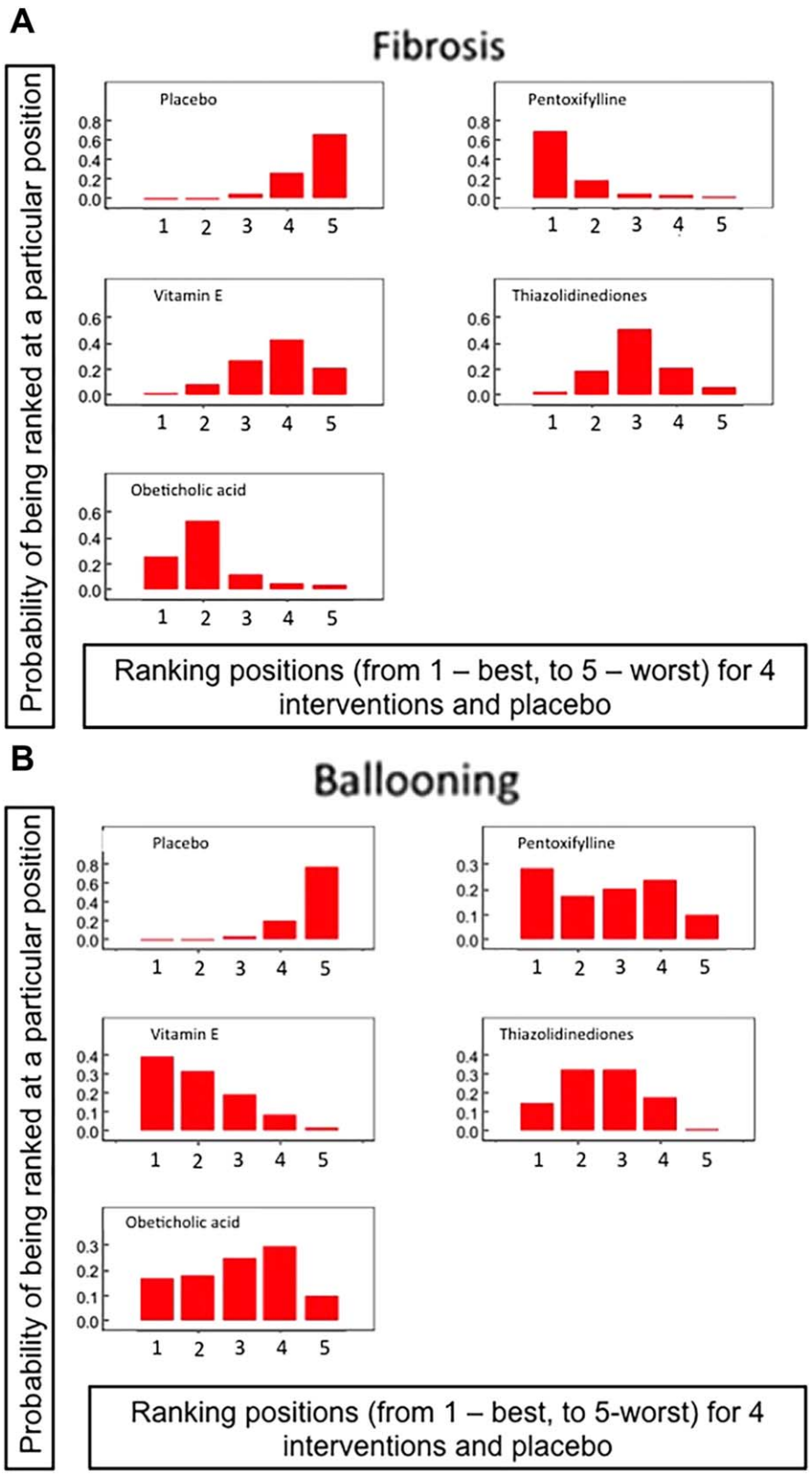

Fig. 3. Ranking probabilities of treatment for NASH, for improvement in (A) fibrosis and (B) ballooning degeneration.

are considerable differences in participants, interventions, cointerventions/background treatment, and outcome assessment, limiting comparability of trials.[12,17] A network meta-analysis assumes that patients enrolled in all included studies could have been sampled from the same theoretical population. Though there may be subtle differences in patient, disease, and treatment characteristics, such as proportion of patients with

cirrhosis or diabetes, baseline disease severity, supportive lifestyle interventions such as diet, exercise, and weight loss, and the rigor with which these were recommended, implemented, and recorded, and so on, we tried to minimize this conceptual heterogeneity by including only studies of pharmacological agents (excluding trials comparing a pharmacological intervention with lifestyle intervention) and assessing robust and multiple histological outcomes at prespecified time points. We used an ITT analysis and imputed missing values using the worst-case scenario (all patients lost to follow-up were considered treatment failures), allowing for conservative imputation of treatment efficacy. We also conducted sensitivity analyses after excluding a pediatric NAFLD study[29] as well as a trial of rosiglitazone in NASH[33]; the overall findings were unchanged, suggesting robustness of the primary analysis. Third, although our protocol accounted for possible reporting of outcomes at multiple time points, we realized that all studies reported only end-of-treatment histological outcomes and had variable follow-up duration. Whereas differences in treatment duration may also influence relative efficacy of different agents, anchoring against a common comparator (in indirect meta-analysis), may partly alleviate these differences. Fourth, publication bias remains a possibility despite the statistical evaluation we have conducted. Finally, ranking probabilities are challenging to interpret, are affected by various factors, such as unequal number of trials per comparison in the network, sample size of individual studies, network configuration, and effect sizes between treatments, and do not always imply a clinically important difference.[56] It is possible that the rank probability for pentoxifylline and OCA (which have the fewest number of trials) may be biased upward, whereas the rank probability for TZDs and vitamin E (which have the highest number of studies) may be underestimated. Hence, in interpreting results from our network meta-analysis, instead of solely focusing on summary estimates and ranking probabilities, we adopted the GRADE approach to rating the quality of evidence from network meta-analysis.

There were similar limitations in the individual studies, which also undermine the strength of the meta-analysis. Most of the studies were small, with limited number of events leading to imprecise estimates. Some studies reported histological improvement as continuous outcomes, without individual participant data, and hence these were not included in our analysis. There was no centralized reading of liver biopsies by an expert hepatopathologist for some trials, which may limit the interpretation of results; however, in all cases, the slides were reviewed by a blinded hepatopathologist and hence less prone to bias. NASH resolution or improvement in NAS, an accepted and multifaceted endpoint,[55] were not uniformly reported in trials, and hence we were unable to use them as outcomes. Long-term safety of these agents was not adequately assessed in RCTs, and hence a thorough assessment of risk-benefit profile could not be performed. Most RCTs excluded patients with cirrhosis or insulin-dependent diabetes, and hence it is difficult to infer on the comparative effectiveness of these agents in this scenario.

Implications for Clinical Practice. Moderate-quality evidence supports the use of pentoxifylline in patients with NASH to improve fibrosis. This is based on two small RCTs of pentoxifylline with low event rates, making the credible intervals fragile; larger randomized studies are warranted to validate these findings. Moreover, only 4%-10% of patients in pentoxifylline trials were diabetics, and it is difficult to extrapolate this benefit to patients with diabetes. High-quality evidence supports the use of vitamin E, TZDs, and OCA in patients with NASH, in improving ballooning degeneration. There has been concern regarding long-term cardiovascular safety of rosiglitazone, though recent evidence suggests that it is safe and the U.S. Food and Drug Administration has eased several previous restrictions on it use.[57] Future comparative trial combination therapies (such as pentoxifylline and pioglitazone or vitamin E) targeting distinct histological features are warranted. In a pilot trial, the combination of vitamin E and pioglitazone was superior to vitamin E alone in improving NASH histology.[45] With the introduction of newer agents such as OCA, cost-effectiveness of these agents also merits consideration.

In conclusion, using network meta-analysis, we observed that pentoxifylline, TZDs, and vitamin E are superior to placebo and comparable to one another for improving key histological features in NASH. OCA also appears promising, though additional data are warranted. Large comparative RCTs, particularly of the combination of pentoxifylline and TZDs/vitamin E, are warranted to further establish the comparative efficacy of different interventions for NASH. This rigorously conducted, unbiased, comprehensive systematic review and network meta-analysis of published trials in NASH would inform the development of future practice guidelines in the treatment of NASH.

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