ネットワークメタ解析から見た
糖尿病重症化予防の薬剤選択
－ネットワークメタ解析の勘所－

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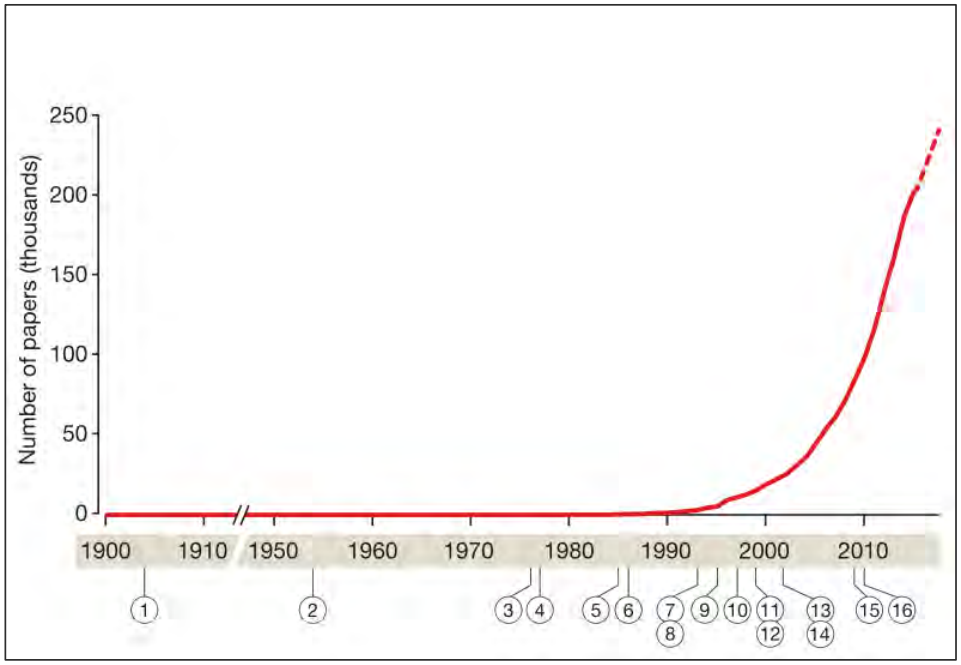
メタ解析の歴史

- 医学分野では90年代以降、メタアナリシスを実施した論文が急増
  - EBM(Evidence Based Medicine)の台頭



1. **1904** First (medical) meta-analysis published (effect of innoculation against typhoid) (ref. 83)
2. **1954** First meta-analytic methods formalized (fixed- and random-effects models) (ref. 86)
3. **1976** Term 'meta-analysis' coined (ref. 95)
4. **1977** First social science meta-analysis published (efficacy of psychotherapy) (ref. 87)
5. **1985** Statistics textbook dedicated to meta-analytic methods released (ref. 16)
6. **1986** Method for calculating between-study variance developed (ref. 96)
7. **1993** Review of 302 social science meta-analyses on treatment efficacy published (ref. 97)
8. **1993** Cochrane Collaboration established
9. **1995** Term 'systematic review' introduced (ref. 98)
10. **1997** Methods for assessing publication bias introduced (funnel plot and Egger's test) (ref. 19)
11. **1999** QUOROM (Quality of Reporting of Meta-analyses) standards developed (ref. 99)
12. **1999** Campbell Collaboration established
13. **2002** Heterogeneity index I^2 proposed (ref. 100)
14. **2002** Term 'network meta-analysis' coined (ref. 74)
15. **2009** PRISMA guidelines established (ref. 12)
16. **2010** *metafor* (free and comprehensive R package for meta-analysis) released (ref. 17)

Gurevitch et al. (Nature, 2018)

メタ解析の歴史

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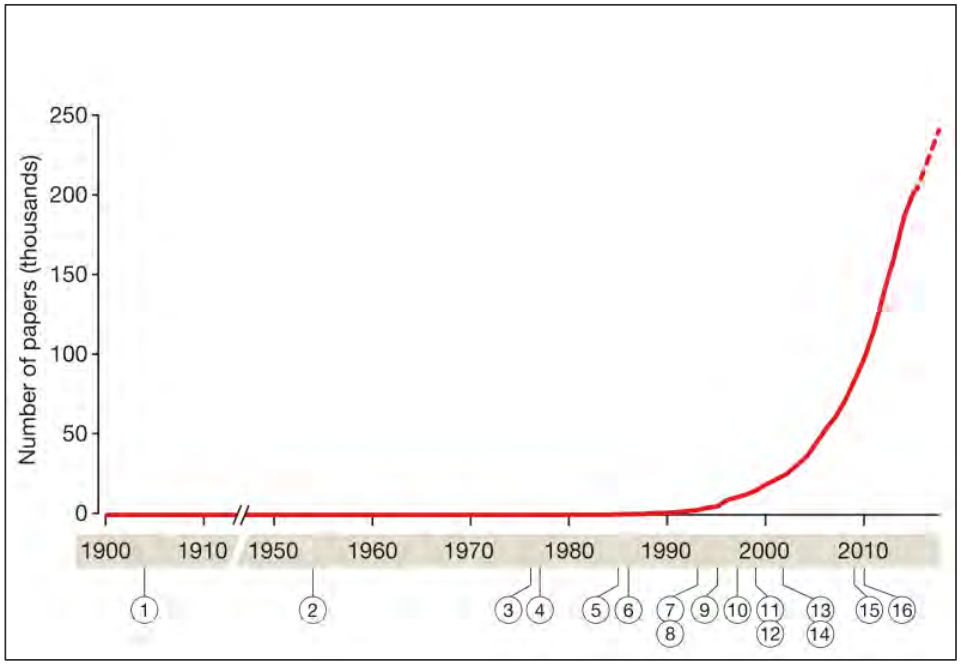

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Network meta-analysisという言葉の出現

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ネットワークメタ解析の報告件数

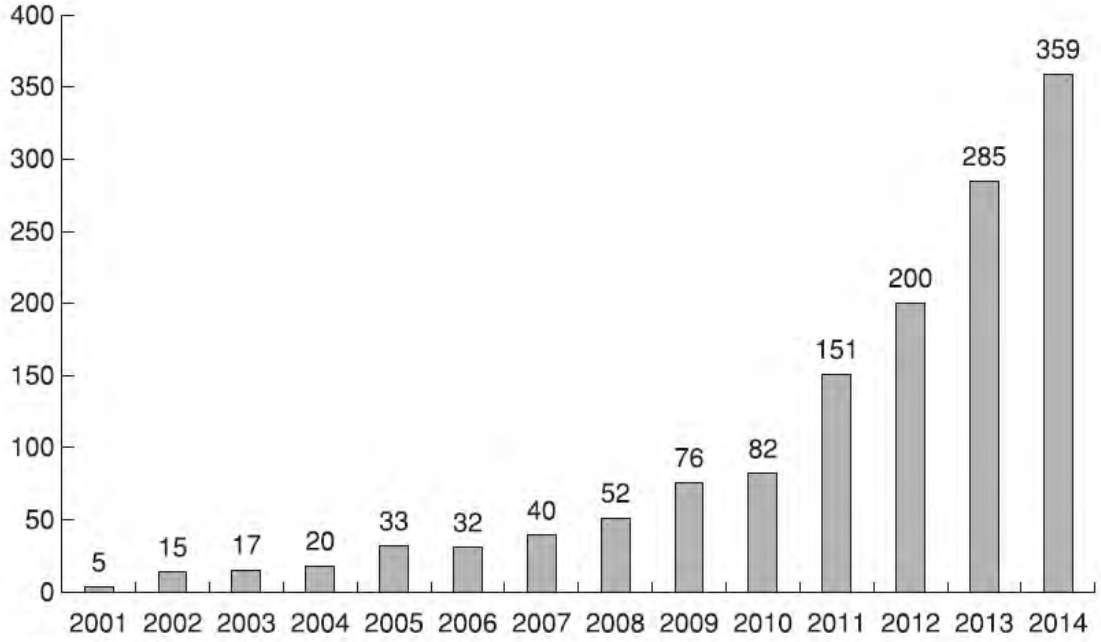


図 3　NMA の論文数

Pubmed で検索（検索式：“network meta-analysis” or “multiple treatment comparison meta-analysis” or “mixed comparison meta-analysis” or “multiple comparison meta-analysis” or “mixed treatment comparison meta-analysis”）

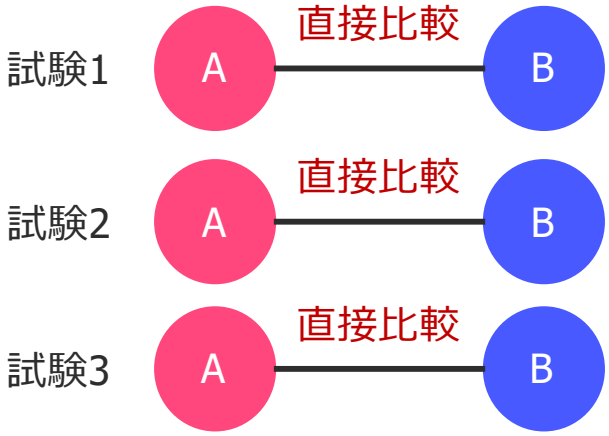
藤井陽介 (薬理と治療, 2015)

従来のメタ解析 (pairwise meta-analysis)

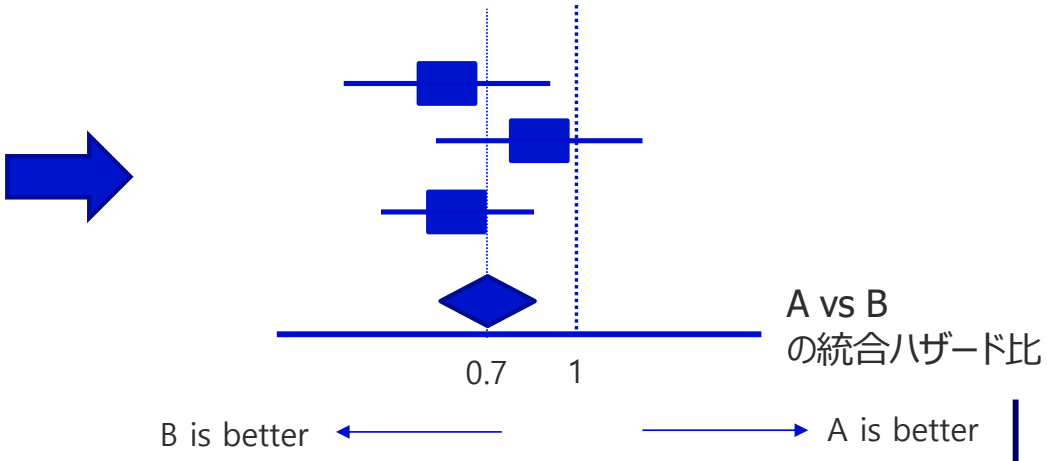
- Patients
- Intervention and control
- Outcome

2型糖尿病患者に対して
DPP-4阻害薬とプラセボを
全生存期間で比較する

特定の比較を対象とした
'従来の'メタアナリシス

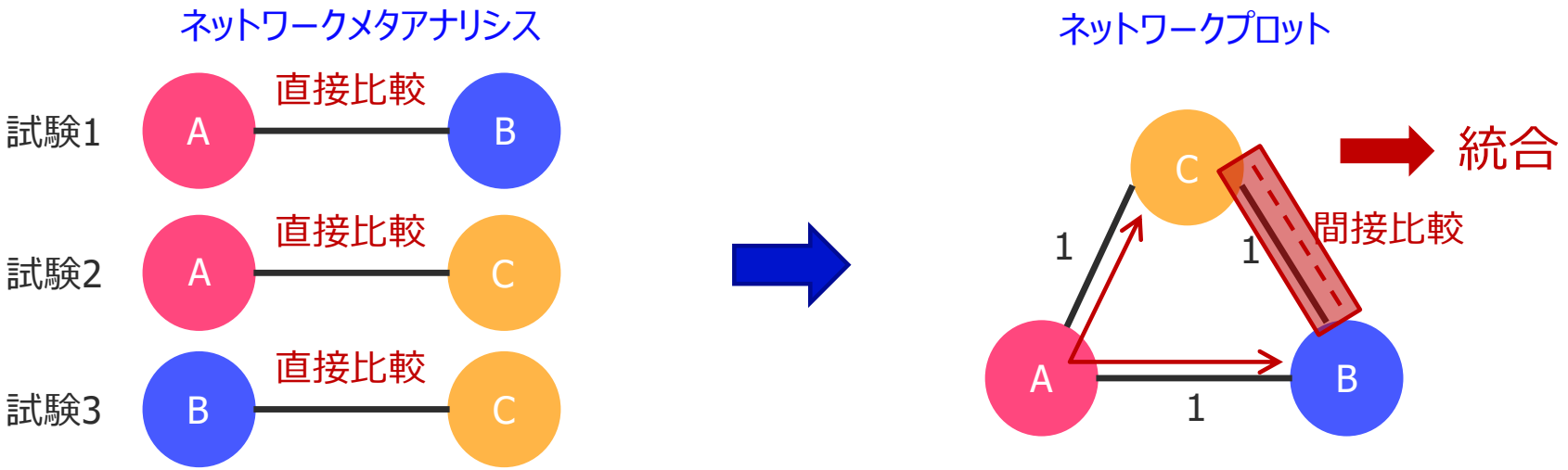


フォレストプロット



ネットワークメタ解析

- 実際には、様々な糖尿病治療薬が承認されている
  - 様々な組み合わせでランダム化比較試験が行われている
  - 全ての直接比較を実施するのには限界がある
- A対Bと、A対Cの結果があれば、ここから間接的にB対Cの結果が得られだろうか？
- B対Cを直接比較した結果もあれば、直接比較と間接比較を統合できないだろうか？
  - ネットワークメタアナリシスは、これらを実現するために考案された解析手法



今日取り上げる事例

Research

JAMA | Original Investigation

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

A Systematic Review and Meta-analysis

Sean L. Zheng, BM BCh, MA, MRCP; Alistair J. Roddick, BSc; Rochan Aghar-Jaffar, BMedSci, BMBS, MRCP; Matthew J. Shun-Shin, BM BCh, MRCP; Darrel Francis, MB BChir, FRCP, MD; Nick Oliver, MBBS, FRCP; Karim Meeran, MBBS, MD, FRCP, FRCPath

Animated Summary Video

Supplemental content

IMPORTANCE The comparative clinical efficacy of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors for treatment of type 2 diabetes is unknown.

OBJECTIVE To compare the efficacies of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors on mortality and cardiovascular end points using network meta-analysis.

DATA SOURCES MEDLINE, Embase, Cochrane Library Central Register of Controlled Trials, and published meta-analyses from inception through October 11, 2017.

STUDY SELECTION Randomized clinical trials enrolling participants with type 2 diabetes and a follow-up of at least 12 weeks were included, for which SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors were compared with either each other or placebo or no treatment.

DATA EXTRACTION AND SYNTHESIS Data were screened by 1 investigator and extracted in duplicate by 2 investigators. A Bayesian hierarchical network meta-analysis was performed.

MAIN OUTCOMES AND MEASURES The primary outcome: all-cause mortality; secondary outcomes: cardiovascular (CV) mortality, heart failure (HF) events, myocardial infarction (MI), unstable angina, and stroke; safety end points: adverse events and hypoglycemia.

RESULTS This network meta-analysis of 236 trials randomizing 176 310 participants found SGLT-2 inhibitors (absolute risk difference [RD], −1.0%; hazard ratio [HR], 0.80 [95% credible interval (CrI), 0.71 to 0.89]) and GLP-1 agonists (absolute RD, −0.6%; HR, 0.88 [95% CrI, 0.81 to 0.94]) were associated with significantly lower all-cause mortality than the control groups. SGLT-2 inhibitors (absolute RD, −0.9%; HR, 0.78 [95% CrI, 0.68 to 0.90]) and GLP-1 agonists (absolute RD, −0.5%; HR, 0.86 [95% CrI, 0.77 to 0.96]) were associated with lower mortality than were DPP-4 inhibitors. DPP-4 inhibitors were not significantly associated with lower all-cause mortality (absolute RD, 0.1%; HR, 1.02 [95% CrI, 0.94 to 1.11]) than were the control groups. SGLT-2 inhibitors (absolute RD, −0.8%; HR, 0.79 [95% CrI, 0.69 to 0.91]) and GLP-1 agonists (absolute RD, −0.5%; HR, 0.85 [95% CrI, 0.77 to 0.94]) were significantly associated with lower CV mortality than were the control groups. SGLT-2 inhibitors were significantly associated with lower rates of HF events (absolute RD, −1.1%; HR, 0.62 [95% CrI, 0.54 to 0.72]) and MI (absolute RD, −0.6%; HR, 0.86 [95% CrI, 0.77 to 0.97]) than were the control groups. GLP-1 agonists were associated with a higher risk of adverse events leading to trial withdrawal than were SGLT-2 inhibitors (absolute RD, 5.8%; HR, 1.80 [95% CrI, 1.44 to 2.25]) and DPP-4 inhibitors (absolute RD, 3.1%; HR, 1.93 [95% CrI, 1.59 to 2.35]).

CONCLUSIONS AND RELEVANCE In this network meta-analysis, the use of SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment.

JAMA. 2018;319(15):1580-1591. doi:10.1001/jama.2018.3024

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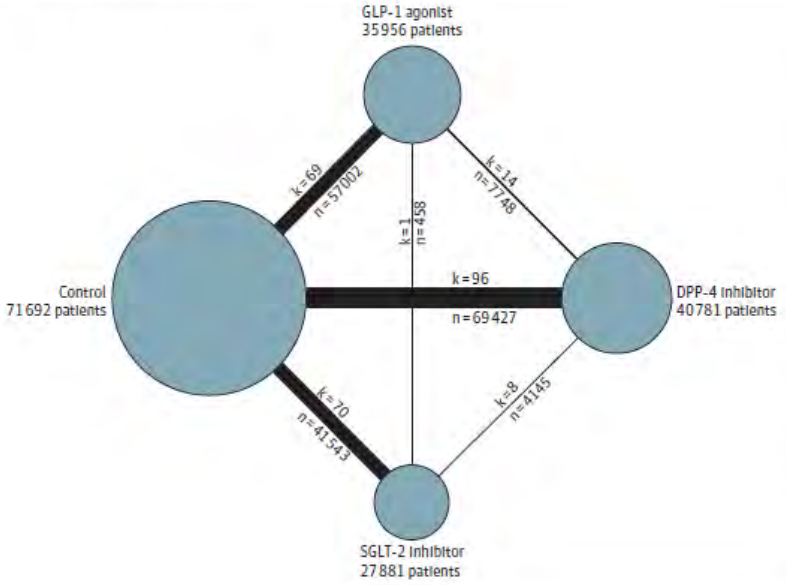
Corresponding Author: Sean L. Zheng, BM BCh, MA, MRCP, Department of Cardiology, Royal Brompton Hospital, Sydney Street, London, UK SW3 6NP (sean.zheng@nhs.net).

Figure 2. Network Plot for All Studies



Graphical representation of network for all included trials. Connecting lines represent head-to-head comparisons between drugs, indicated by nodes. Multigroup trials contribute multiple comparisons, resulting in 258 comparisons from 236 trials. The thickness of lines between nodes is proportional to the number of trials comparing the treatments. The sizes of the nodes are proportional to the number of patients in each treatment. Patients may be included in multiple comparisons: for example, in a study of 3 groups consisting of control and 2 different drug classes, the control group is compared with each drug class. This is accounted for within the network model and does not constitute duplication of participants.

DPP-4 indicates dipeptidyl peptidase 4 GLP-1, glucagon-like peptide 1; k, the number of comparisons; n, the number of patients per comparison; and SGLT-2, sodium-glucose cotransporter 2.

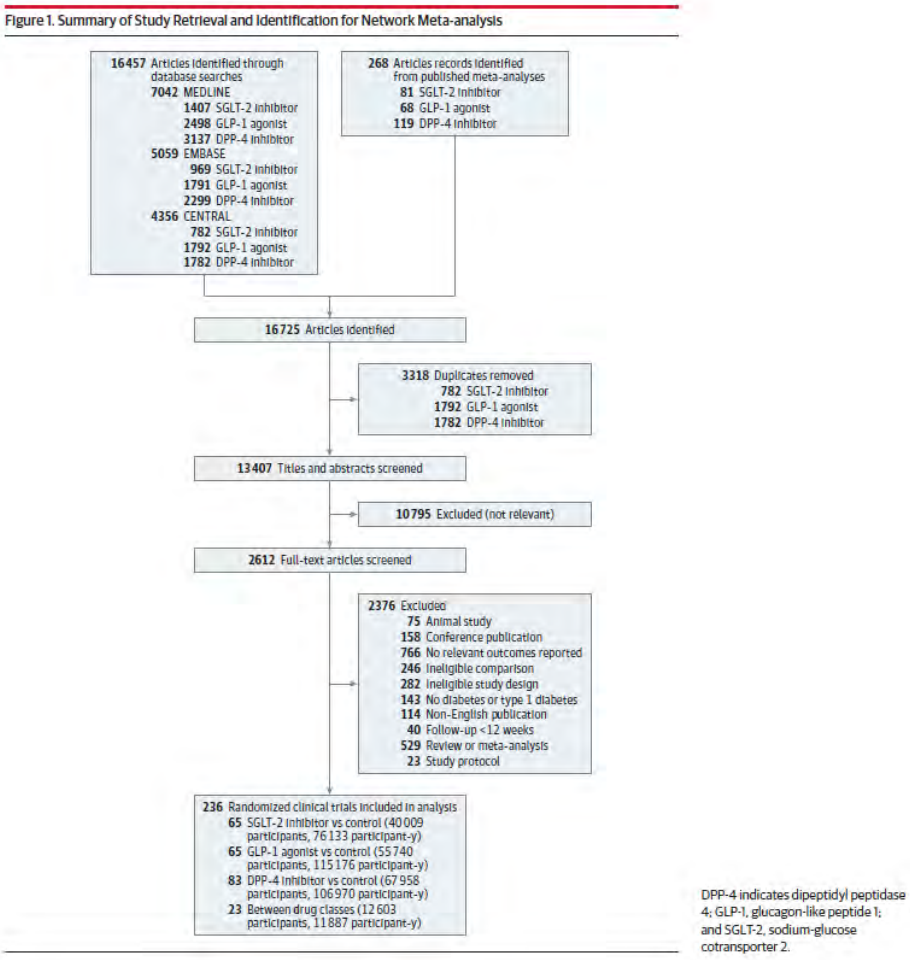
Zheng SL et al, JAMA 2018

JAMA論文における研究目的

- 2型糖尿病患者を対象に
- SGLT-2阻害薬、GLP-1受容体作動薬、DPP-4阻害薬、コントロール治療の間で
- 主要エンドポイント：全生存期間（総死亡）
- 副次エンドポイント：循環器死亡、心不全、心筋梗塞、不安定狭心症、脳卒中
- 安全性エンドポイント：有害事象、低血糖
- ネットワークメタ解析の手法を用いて、比較を行う

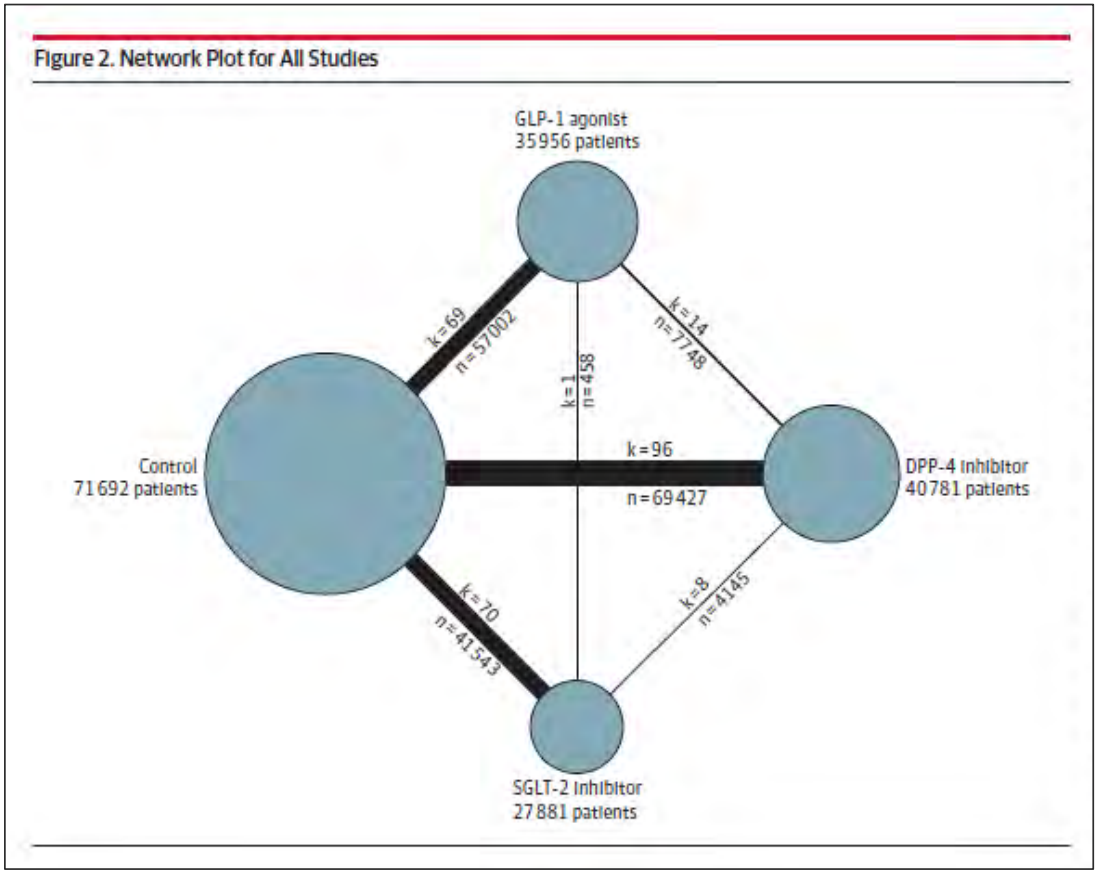
Palmerini T et al, Lancet 2012

対象となった試験のフローダイアグラム



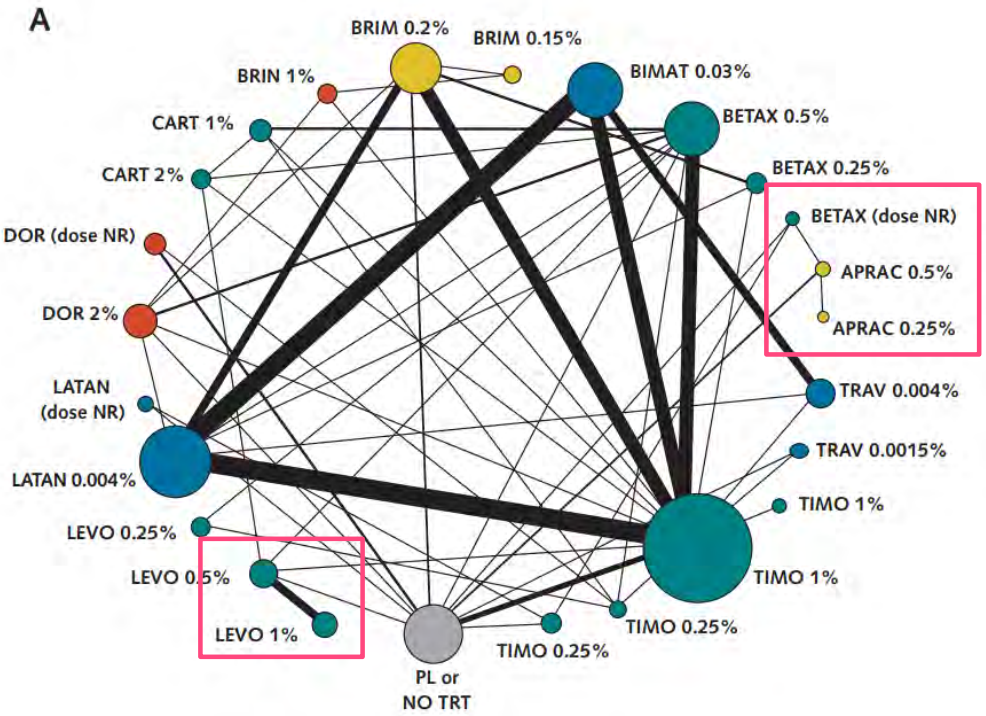
- 対象試験
  - プラセボ・無治療とSGLT-2、GLP-1、DPP-4を比較したランダム化比較試験
  - 最低12か月以上の追跡
  - 目的としたエンドポイントを評価
- 検索の正確性・再現性の担保
- 最終的に236試験が解析対象

ネットワークプロット



- 対象となった試験の関係性をグラフ化
- ノード（集合点：各治療群）と
  エッジ（辺：直接比較の存在）で
  構成されるプロット

他の研究のネットワークプロット



- ノードの大きさを個々の治療群のサンプルサイズの総数に比例して表示
- エッジの太さを個々の直接比較のサンプルサイズの総数に比例して表示
- それぞれの治療群・直接比較が、全体の結果にどの程度、寄与するかを理解するために有用なプロット
- Triangle Loopを形成しない孤立したノードは、間接比較のエビデンスを共有できないため、直接比較のエビデンス以上に情報量の増加はなく、比較的不安定な結果が得られやすいので注意！

PRISMA NMA, Ann Int Med 2015

Statistical analysis（抜粋）

- Network meta-analysis comprises direct and indirect comparisons between multiple interventions, allowing comparisons to be made when direct trial evidence is scarce (乏しい).
  - This approach respects randomization but does not represent randomized evidence.
- A Bayesian hierarchical network meta-analysis was performed … Fixed- or random-effects models were selected for each outcome based on the deviance information criterion (DIC).
- Analyses were performed using Markov-chain Monte Carlo methods. Results were presented as hazard ratios (HRs) with 95% credible intervals (CrIs).

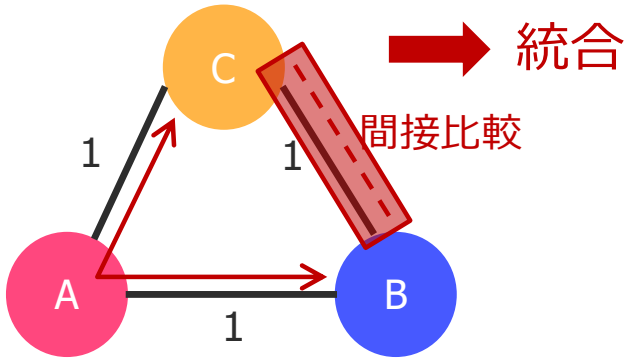
詳細な記載の内容は生物統計の専門家と
協力して読み解く必要あり

ネットワークメタ解析の肝 

- 直接比較(direct comparison)の統合
  - 通常のメタ解析で実施される、同じ比較を行っているRCTの統合
  - 網羅的に論文が把握され、それぞれの試験の質が良く、結果が類似していれば、統合結果で得られるエビデンスの説得力は強い
- 直接比較と間接比較(indirect comparison)の統合
  - ネットワークメタアナリシスにおける肝となる部分
- 統合が可能と考えられる前提とは？
  - 網羅的に論文が把握され、それぞれの試験の質が良く、直接比較の結果と間接比較の結果が類似していれば、統合結果で得られるエビデンスの説得力は強い
  - consistency assumption (一致性の仮定)

一致性の仮定

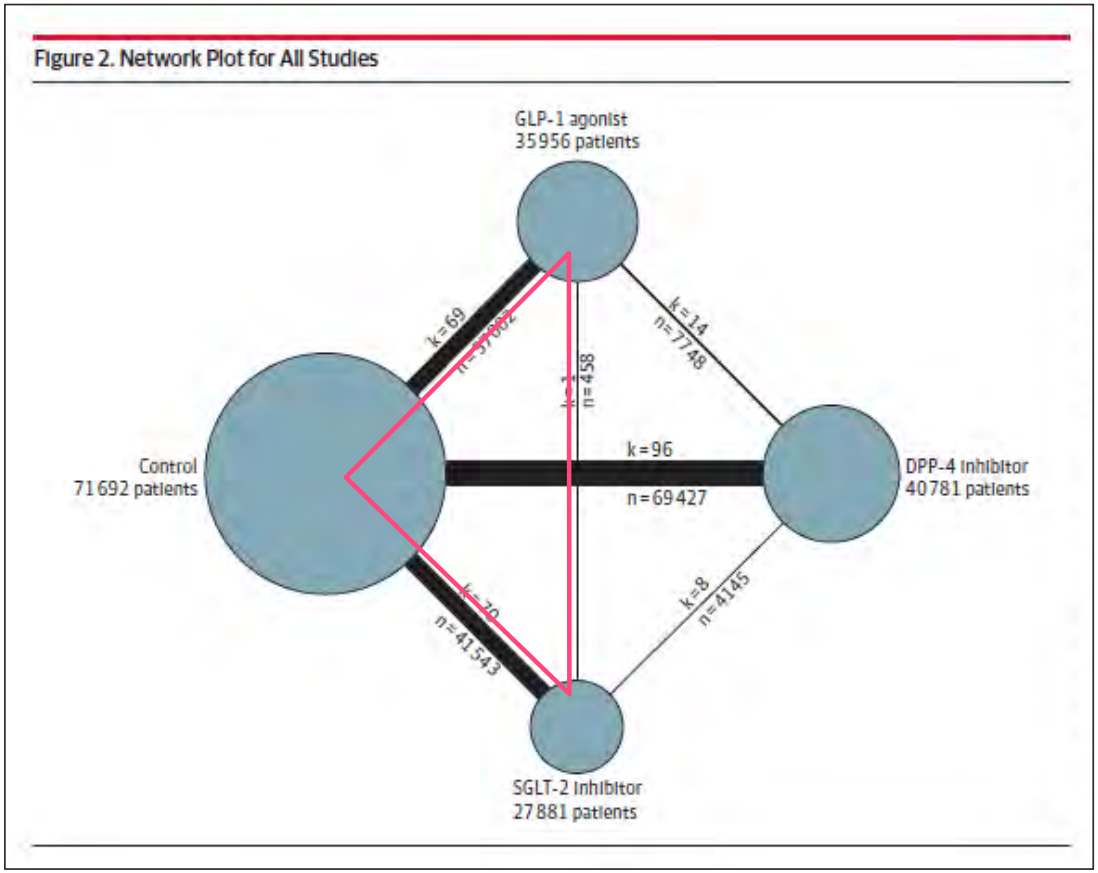
- ネットワークの全てのパスにおいて、直接比較と間接比較の効果の大きさが一致する(consistentである)こと



B vs Cの結果：ハザード比=0.80
A vs C, A vs Bからの間接的な結果: ハザード比=0.75
➡ 結果的に整合しているのであれば、統合可能

B vs Cの結果：ハザード比=0.80
A vs C, A vs Bからの間接的な結果: ハザード比=2.00
➡ 結果的に不一致が見られる
➡ ネットワーク上の比較の妥当性が失われているのでは？
➡ Inconsistencyが生じている

一致性の評価



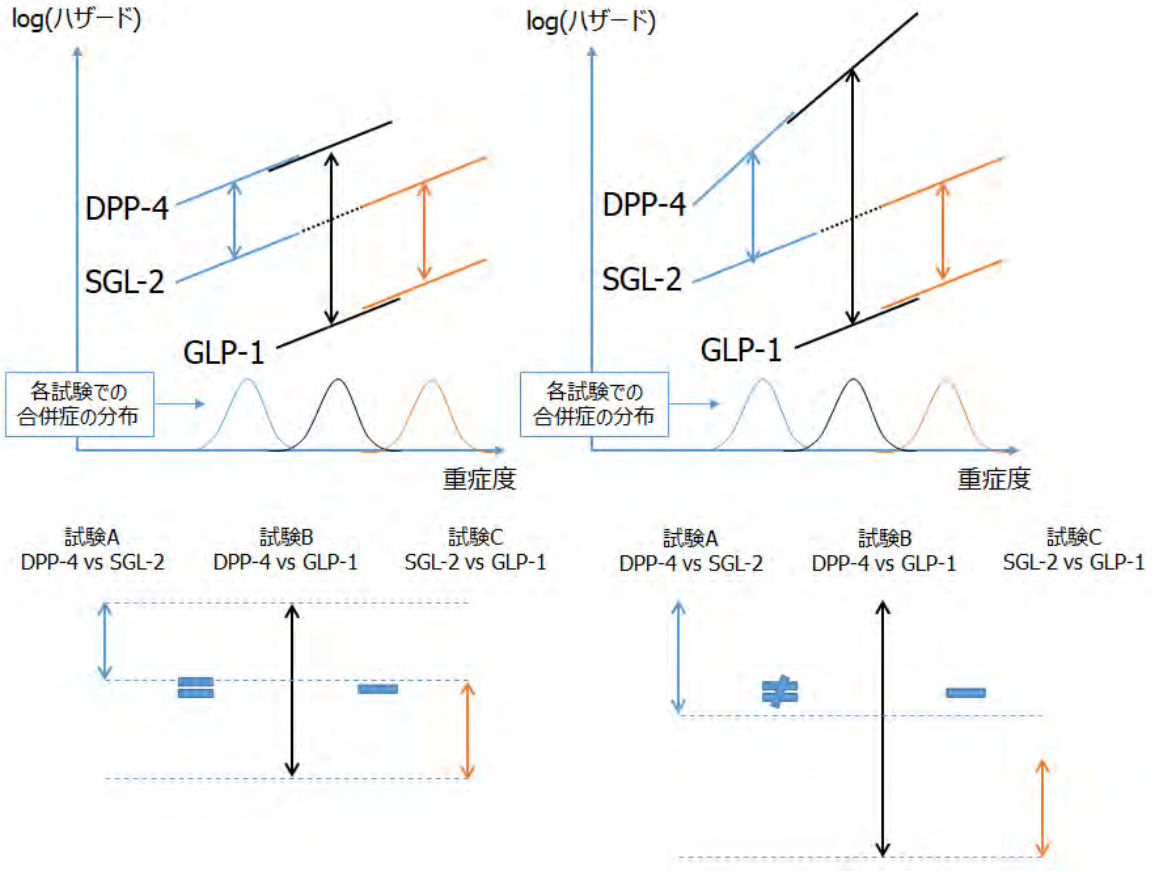
- ネットワーク上の特定のTriangleに対して直接比較と間接比較がconsistentか？
- 局所的な一致性の程度は、

$$\frac{\text{直接比較の効果} - \text{間接比較の効果}}{\sqrt{\text{直接比較の分散} + \text{間接比較の分散}}} \sim N(1,0)$$

のような検定で評価することが可能

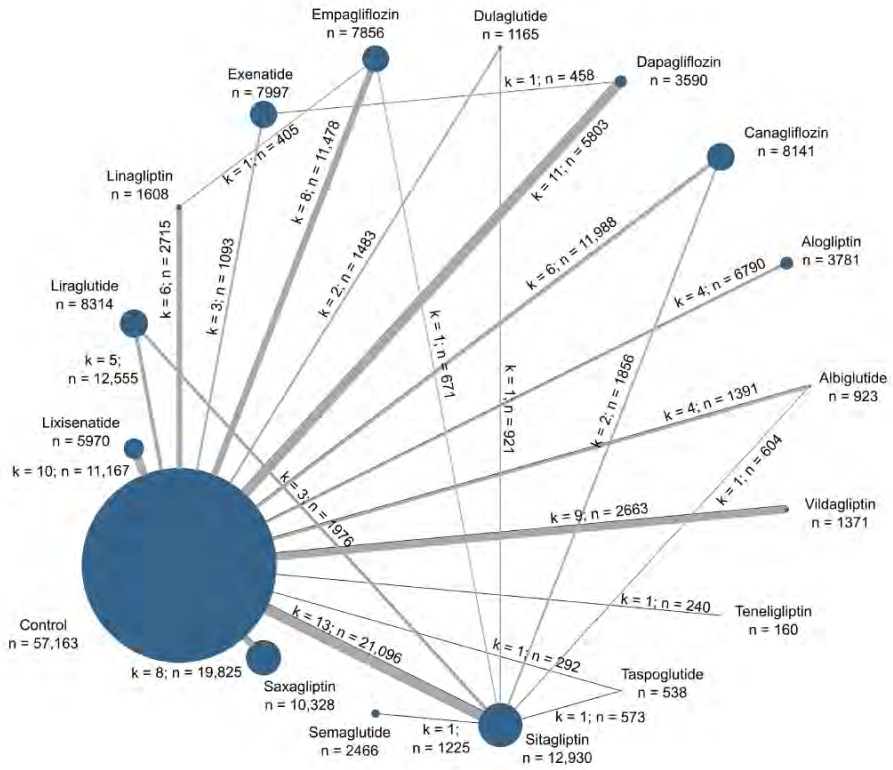
- ネットワークメタ解析は、ネットワーク上の全ての統合に一致性を仮定しているので、1つでも崩れると妥当性が成り立たない
  - ネットワーク全体の一致性も評価

どういった時にinconsistencyが生じる？



- 治療との交互作用を示すような背景因子が試験間で異なる場合
  - 右図の状況
- DPP-4が重症度が高くなれば、心不全リスクが、他の薬よりも、より起きやすくなる
  - 直接比較と間接比較の結果は系統的にズレる
- 交互作用を起こしうる要因
  - 個人レベルの特性: 年齢、疾患重症度、合併症など
  - 試験レベルの特性: 治療計画、治療環境、時代効果、など

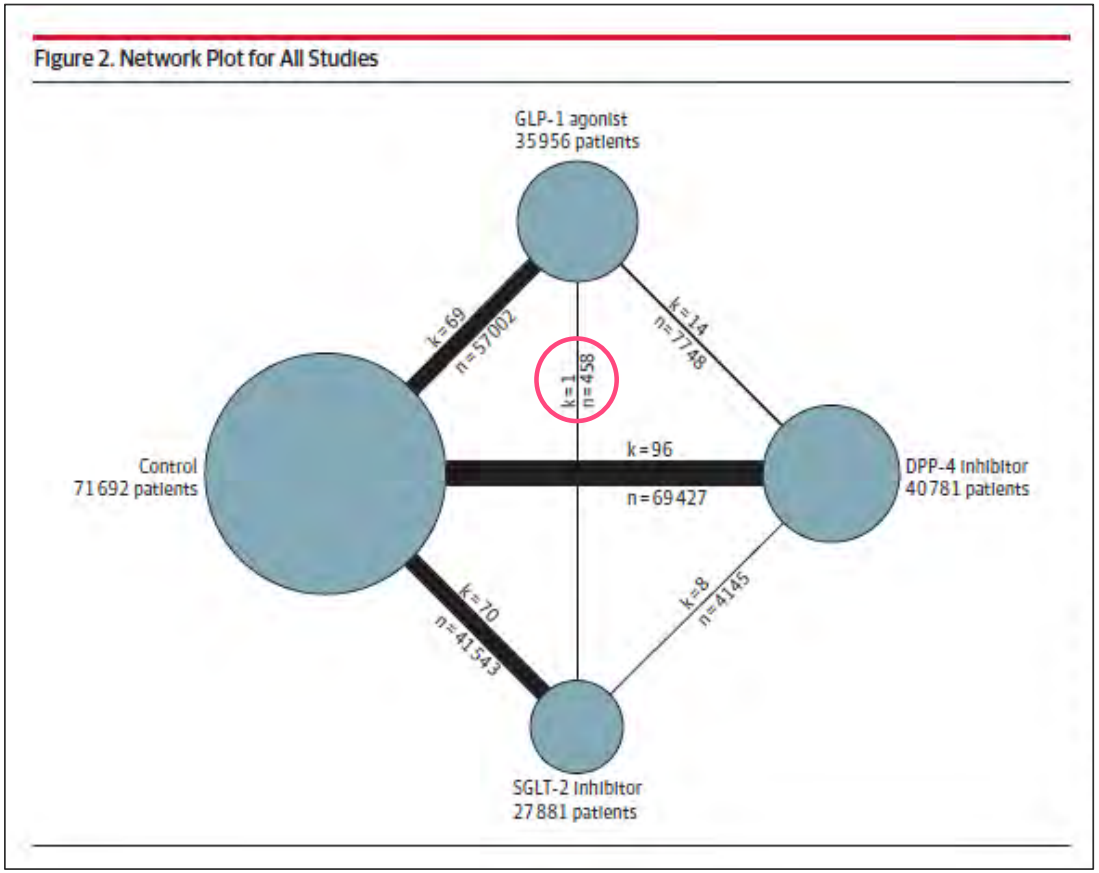
結果の確認：薬剤間の比較



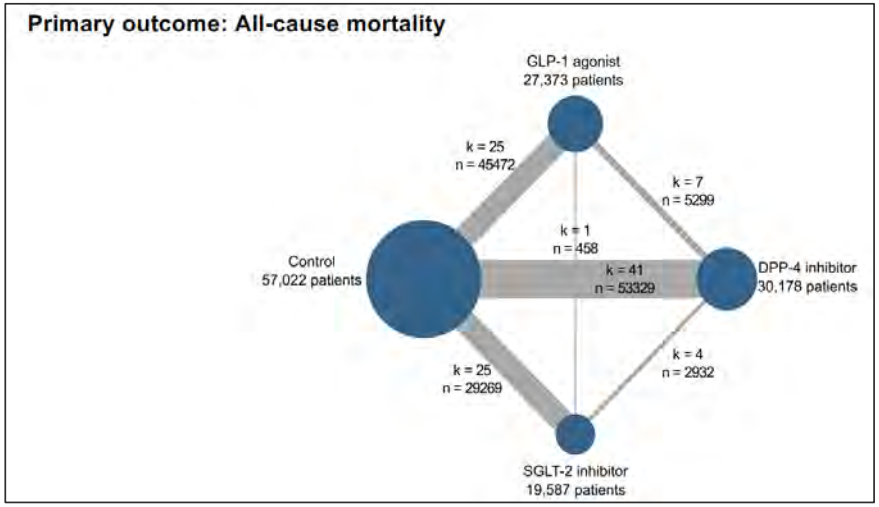
- 薬剤間の比較は、信用できる結果は得られなさそうであることが分かる

Zheng SL et al, JAMA 2018: eFigure5

結果の確認：薬剤クラス間の比較



- クラス間比較については、十分な数の直接比較が存在
  - ただし、SGLT-2とGLP-1の直接比較は1試験のみ
- アウトカムよってプロットは変わることに注意



Zheng SL et al, JAMA 2018: Figure2, eFigure3

結果の確認：直接比較における背景

Table. Study Participant Characteristics[a]

Drug Type	No. of Trials	Total No. Randomized	Mean (SD)			
			Men, %	Age, y	BMI	HbA_{1c}, %
DPP-4 inhibitor vs control	83	67 958	54.7 (9.4)	57.9 (5.3)	29.3 (2.9)	8.16 (0.61)
GLP-1 agonist vs control	65	55 740	55.1 (11.4)	57.1 (3.8)	31.5 (3.5)	8.11 (0.36)
SGLT-2 inhibitor vs control	65	40 009	57.9 (10.4)	58.0 (3.7)	29.3 (5.0)	8.05 (0.32)
DPP-4 inhibitor vs GLP-1 agonist	14	8024	50.9 (7.5)	52.9 (4.4)	32.6 (2.3)	8.2 (0.20)
DPP-4 inhibitor vs SGLT-2 inhibitor	8	4121	56.0 (5.5)	55.5 (2.1)	30.9 (1.2)	8.0 (0.39)
GLP-1 agonist vs SGLT-2 inhibitor	1	458				

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HbA_{1c}, hemoglobin A_{1c}; SLGT2, sodium-glucose cotransporter 2.

[a] The Table represents data from studies stratified by the intervention and comparator. Control refers to placebo or no treatment. There was 1 study assessing GLP-1 agonist compared with a SGLT-2 inhibitor.

DPP-4 vs SGLT-2の比較だけ、少し集団が異なるが、概ね類似

Zheng SL et al, JAMA 2018: Table

結果の確認：全死亡について、一致性の確認

All-cause mortality

Comparison	Events	Trials	Evidence	HR (95% CrI)	RoR (95% CI)	P-value
DPP4:GLP1	20	7	Direct	0.59 (0.24-1.47)	0.76 (0.28-2.10)	0.60
			Indirect	0.86 (0.77-0.97)		
DPP4:Control	2288	41	Direct	0.98 (0.90-1.07)	1.17 (0.27-5.11)	0.83
			Indirect	0.82 (0.32-2.21)		
DPP4:SGLT2	6	4	Direct	1.38 (0.25-11.23)	1.82 (0.20-16.68)	0.60
			Indirect	0.78 (0.68-0.90)		
GLP1:Control	2520	25	Direct	1.14 (1.06-1.23)	0.68 (0.05-9.35)	0.78
			Indirect	1.52 (0.56-4.06)		
GLP1:SGLT2	4	1	Direct	0.26 (0.01-2.45)	0.52 (0.05-5.62)	0.59
			Indirect	0.92 (0.80-1.05)		
Control:SGLT2	1207	25	Direct	0.80 (0.71-0.89)	0.86 (0.04-20.28)	0.93
			Indirect	0.95 (0.24-3.99)		

Zheng SL et al, JAMA 2018: eFigure9

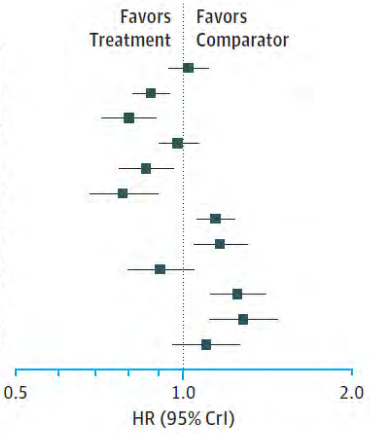
メインの結果

- 全ての組み合わせのフォレストプロット
- GLP-1とSGLT-2はコントロールよりも死亡を抑制
  - ハザード比が、0.88、080
  - リスク差が-0.6%、-1.0%なので、Number Needed to Treatは、166.7、100.0人
- GLP-1とSGLT-2はDPP-4よりも死亡を抑制
  - ハザード比が、0.86、0.78

A Primary outcome: all-cause mortality, 97 trials; $I^2 = 12\%$

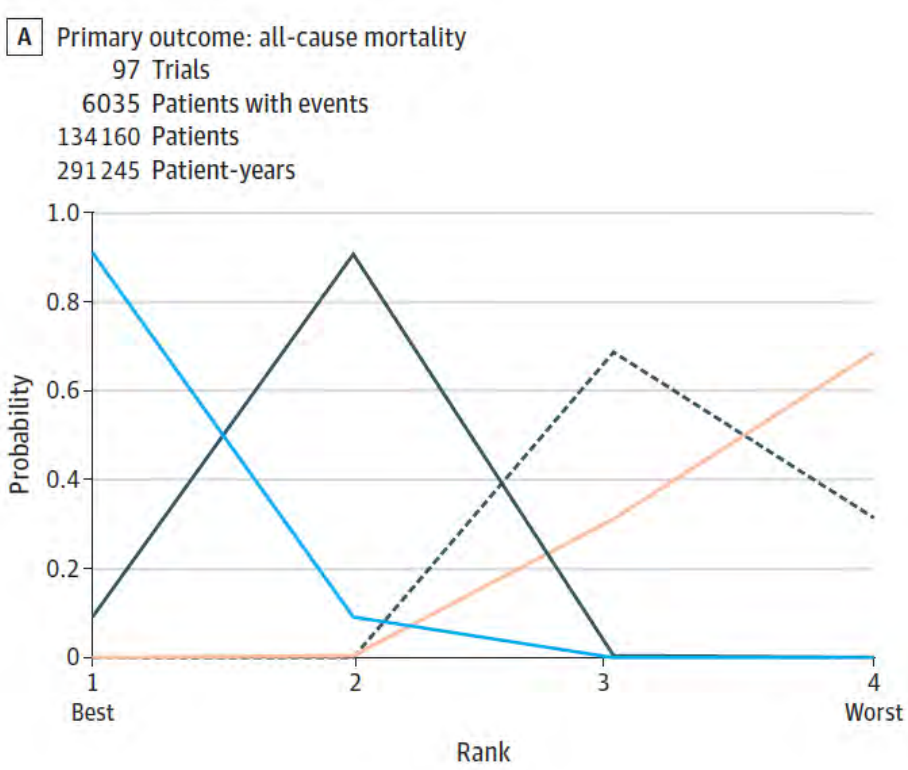
Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.1 (-0.3 to 0.6)	1.02 (0.94 to 1.11)
GLP-1 agonist		-0.6 (-1.0 to -0.3)	0.88 (0.81 to 0.94)
SGLT-2 inhibitor		-1.0 (-1.5 to -0.6)	0.80 (0.71 to 0.89)
Control	vs DPP-4 inhibitor	-0.1 (-0.4 to 0.2)	0.98 (0.90 to 1.06)
GLP-1 agonist		-0.5 (-0.9 to -0.2)	0.86 (0.77 to 0.96)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.4)	0.78 (0.68 to 0.90)
Control	vs GLP-1 agonist	0.6 (0.3 to 1.0)	1.14 (1.06 to 1.23)
DPP-4 inhibitor		0.7 (0.2 to 1.3)	1.17 (1.04 to 1.30)
SGLT-2 inhibitor		-0.4 (-0.9 to 0.2)	0.91 (0.79 to 1.04)
Control	vs SGLT-2 inhibitor	0.9 (0.4 to 1.5)	1.25 (1.12 to 1.40)
DPP-4 inhibitor		1.0 (0.4 to 1.7)	1.28 (1.11 to 1.47)
GLP-1 agonist		0.4 (-0.1 to 0.9)	1.10 (0.96 to 1.26)

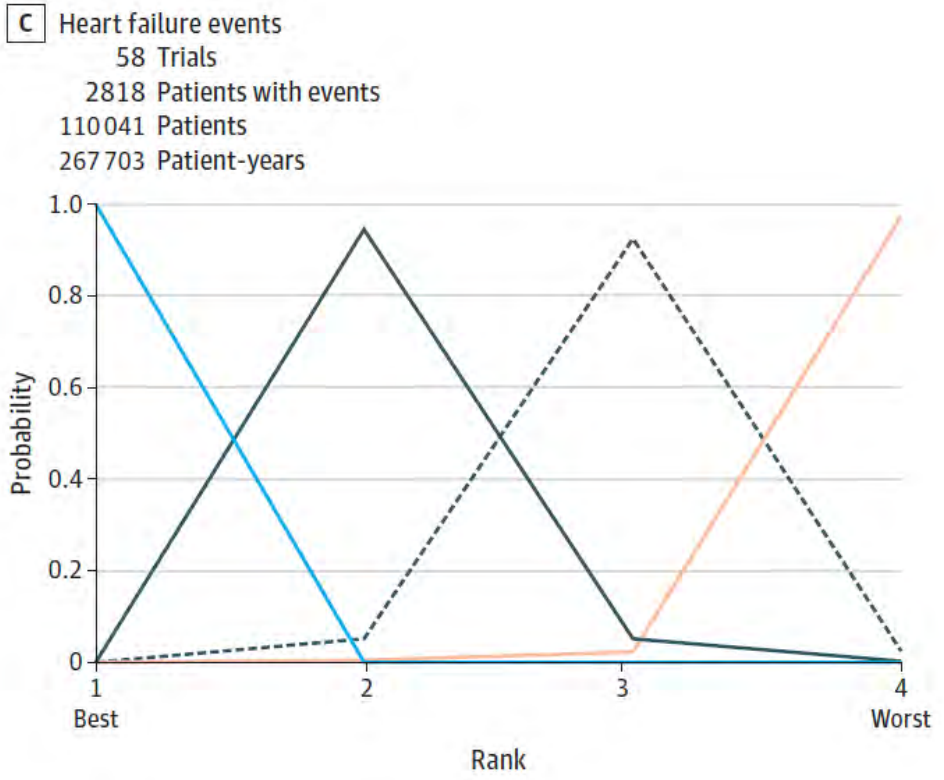
Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	88	2955 (5.2)	57022
DPP-4 inhibitor	49	1171 (3.9)	30178
GLP-1 agonist	32	1195 (4.4)	27373
SGLT-2 inhibitor	29	714 (3.6)	19587



Zheng SL et al, JAMA 2018: Figure3

その他結果提示例：ランキング





Zheng SL et al, JAMA 2018: Figure5

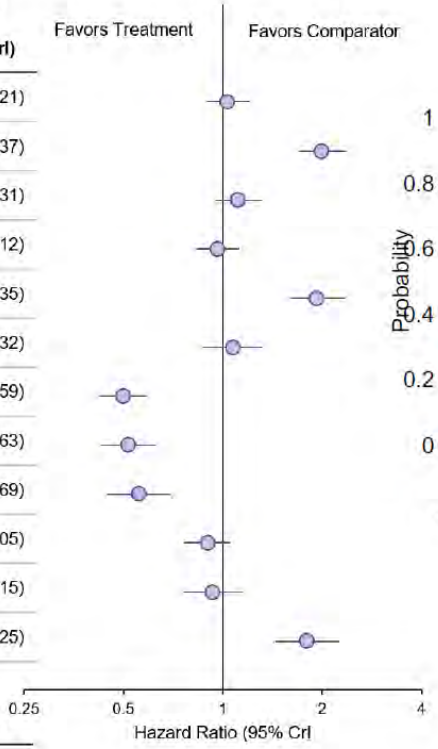
他のエンドポイント：中止に至った有害事象

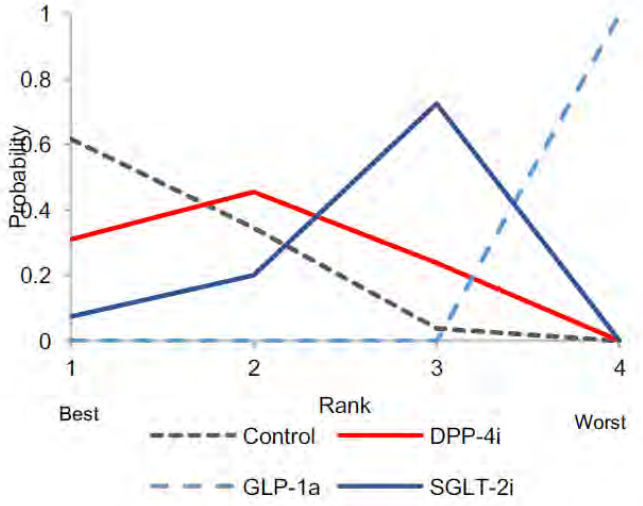
Adverse events leading to withdrawal (Random-effects)

Treatment	Comparator	ARD (95% CI)	HR (95% CrI)
DPP-4 inhibitor		+0.2% (-0.5% to +1.0%)	1.04 (0.89-1.21)
GLP-1 agonist	vs Control	+4.7% (+3.3% to +6.5%)	2.00 (1.70-2.37)
SGLT-2 inhibitor		+0.5% (-0.2% to +1.5%)	1.11 (0.95-1.31)
Control		-0.1% (-0.6% to +0.4%)	0.97 (0.83-1.12)
GLP-1 agonist	vs DPP-4 inhibitor	+3.1% (+2.0% to +4.5%)	1.93 (1.59-2.35)
SGLT-2 inhibitor		+0.2% (-0.4% to +1.1%)	1.07 (0.87-1.32)
Control		-3.5% (-4.1% to -2.9%)	0.50 (0.42-0.59)
DPP-4 inhibitor	vs GLP-1 agonist	-3.4% (-4.0% to -2.6%)	0.52 (0.43-0.63)
SGLT-2 inhibitor		-3.1% (-4.0% to -2.2%)	0.56 (0.44-0.69)
Control		-0.7% (-1.7% to +0.4%)	0.90 (0.76-1.05)
DPP-4 inhibitor	vs SGLT-2 inhibitor	-0.5% (-1.7% to +1.1%)	0.93 (0.76-1.15)
GLP-1 agonist		+5.8% (+3.2% to +9.0%)	1.80 (1.44-2.25)

186 trials; I^2 = 4%

Treatment	Number of trials	Events (%)	Total Patients
Control	172	2112 (4.7)	44,766
DPP-4 inhibitor	86	659 (3.4)	19,620
GLP-1 agonist	60	2278 (7.1)	32,094
SGLT-2 inhibitor	64	1584 (7.2)	21,921

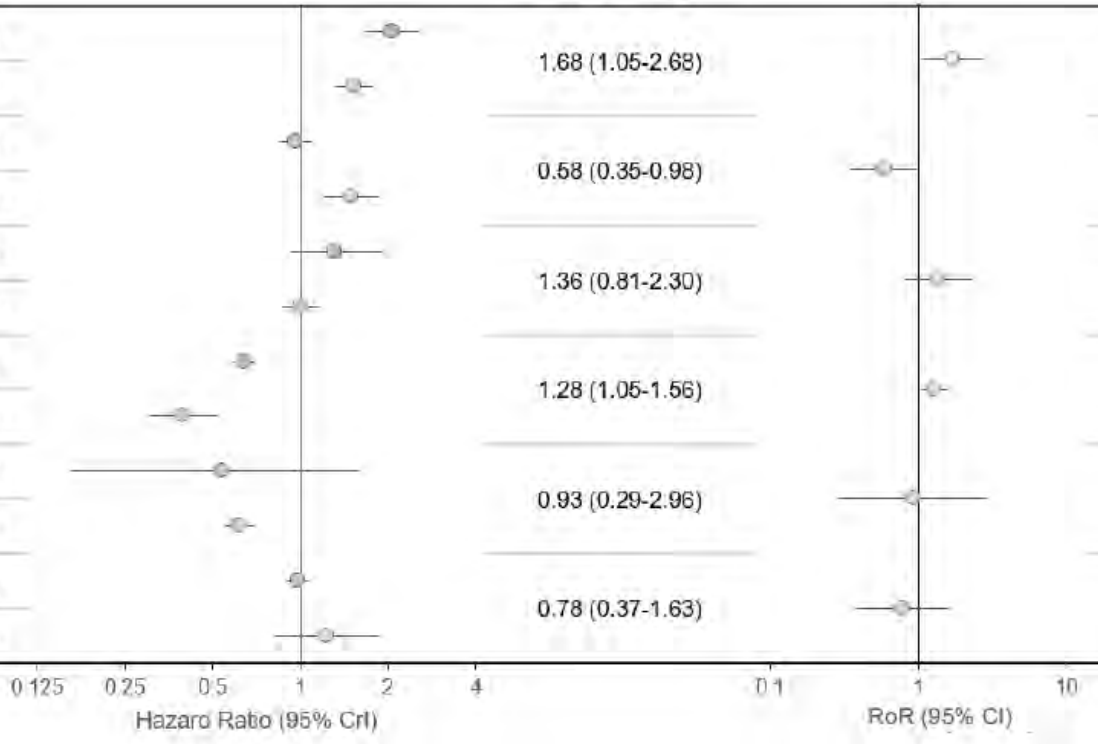




一致性の確認

Adverse events leading to withdrawal

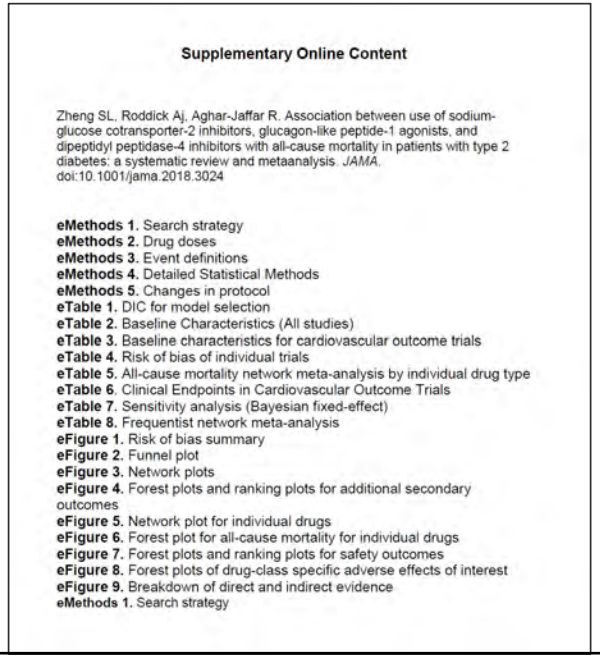
Comparison	Events	Trials	Evidence	HR (95% CrI)	RoR (95% CI)	P-value
DPP4:GLP1	510	12	Direct	2.05 (1.68-2.53)	1.68 (1.05-2.68)	0.03
			Indirect	1.53 (1.31-1.79)		
DPP4:Control	898	71	Direct	0.96 (0.83-1.10)	0.58 (0.35-0.98)	0.04
			Indirect	1.50 (1.20-1.88)		
DPP4:SGLT2	152	8	Direct	1.31 (0.92-1.89)	1.36 (0.81-2.30)	0.25
			Indirect	1.00 (0.87-1.16)		
GLP1:Control	2902	48	Direct	0.64 (0.59-0.69)	1.28 (1.05-1.56)	0.02
			Indirect	0.39 (0.30-0.52)		
GLP1:SGLT2	14	1	Direct	0.53 (0.16-1.59)	0.93 (0.29-2.96)	0.90
			Indirect	0.61 (0.55-0.68)		
Control:SGLT2	2351	59	Direct	0.98 (0.90-1.07)	0.78 (0.37-1.63)	0.50
			Indirect	1.23 (0.81-1.88)		



ネットワークメタ解析を読み解くには…

- 背景の違い、それによって生じる交互作用の可能性
- 直接比較、間接比較の一致性の確認
- 有意かどうかより、効果の大きさがどの程度か、という確認
  - 臨床的に意味があるか、また、医療経済的に利用する価値があるか

- 附録も読む必要がある
- 今回の論文であれば、88ページ
  - 100ページを超えることも稀ではない

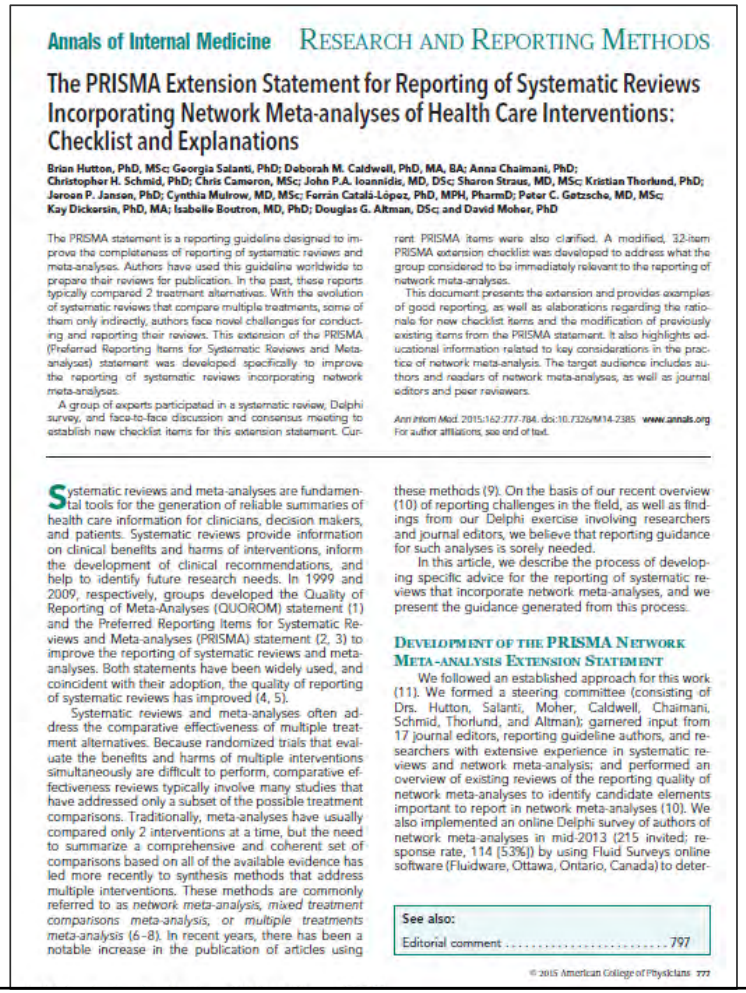


Supplementary Online Content

Zheng SL, Roddick Aj, Aghar-Jaffar R. Association between use of sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 agonists, and dipeptidyl peptidase-4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and metaanalysis. *JAMA*. doi:10.1001/jama.2018.3024

eMethods 1. Search strategy
eMethods 2. Drug doses
eMethods 3. Event definitions
eMethods 4. Detailed Statistical Methods
eMethods 5. Changes in protocol
eTable 1. DIC for model selection
eTable 2. Baseline Characteristics (All studies)
eTable 3. Baseline characteristics for cardiovascular outcome trials
eTable 4. Risk of bias of individual trials
eTable 5. All-cause mortality network meta-analysis by individual drug type
eTable 6. Clinical Endpoints in Cardiovascular Outcome Trials
eTable 7. Sensitivity analysis (Bayesian fixed-effect)
eTable 8. Frequentist network meta-analysis
eFigure 1. Risk of bias summary
eFigure 2. Funnel plot
eFigure 3. Network plots
eFigure 4. Forest plots and ranking plots for additional secondary outcomes
eFigure 5. Network plot for individual drugs
eFigure 6. Forest plot for all-cause mortality for individual drugs
eFigure 7. Forest plots and ranking plots for safety outcomes
eFigure 8. Forest plots of drug-class specific adverse effects of interest
eFigure 9. Breakdown of direct and indirect evidence
eMethods 1. Search strategy

ネットワークメタアナリシスを読むときの参考に



Annals of Internal Medicine RESEARCH AND REPORTING METHODS

The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations

Brian Hutton, PhD, MSc; Georgia Salanti, PhD; Deborah M. Caldwell, PhD, MA, BA; Anna Chaimani, PhD; Christopher H. Schmid, PhD; Chris Cameron, MSc; John P.A. Ioannidis, MD, DSc; Sharon Straus, MD, MSc; Kristian Thorlund, PhD; Jeroen P. Jansen, PhD; Cynthia Mulrow, MD, MSc; Ferrán Catalá-López, PhD, MPH, PharmD; Peter C. Gøtzsche, MD, MSc; Kay Dickersin, PhD, MA; Isabelle Boutron, MD, PhD; Douglas G. Altman, DSc; and David Moher, PhD

The PRISMA statement is a reporting guideline designed to improve the completeness of reporting of systematic reviews and meta-analyses. Authors have used this guideline worldwide to prepare their reviews for publication. In the past, these reports typically compared 2 treatment alternatives. With the evolution of systematic reviews that compare multiple treatments, some of them only indirectly, authors face novel challenges for conducting and reporting their reviews. This extension of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement was developed specifically to improve the reporting of systematic reviews incorporating network meta-analyses.

A group of experts participated in a systematic review, Delphi survey, and face-to-face discussion and consensus meeting to establish new checklist items for this extension statement. Current PRISMA items were also clarified. A modified, 32-item PRISMA extension checklist was developed to address what the group considered to be immediately relevant to the reporting of network meta-analyses.

This document presents the extension and provides examples of good reporting, as well as elaborations regarding the rationale for new checklist items and the modification of previously existing items from the PRISMA statement. It also highlights educational information related to key considerations in the practice of network meta-analysis. The target audience includes authors and readers of network meta-analyses, as well as journal editors and peer reviewers.

Ann Intern Med. 2015;162:777-784. doi:10.7326/M14-2385 www.annals.org
For author affiliations, see end of text.

Systematic reviews and meta-analyses are fundamental tools for the generation of reliable summaries of health care information for clinicians, decision makers, and patients. Systematic reviews provide information on clinical benefits and harms of interventions, inform the development of clinical recommendations, and help to identify future research needs. In 1999 and 2009, respectively, groups developed the Quality of Reporting of Meta-Analyses (QUOROM) statement (1) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (2, 3) to improve the reporting of systematic reviews and meta-analyses. Both statements have been widely used, and coincident with their adoption, the quality of reporting of systematic reviews has improved (4, 5).

Systematic reviews and meta-analyses often address the comparative effectiveness of multiple treatment alternatives. Because randomized trials that evaluate the benefits and harms of multiple interventions simultaneously are difficult to perform, comparative effectiveness reviews typically involve many studies that have addressed only a subset of the possible treatment comparisons. Traditionally, meta-analyses have usually compared only 2 interventions at a time, but the need to summarize a comprehensive and coherent set of comparisons based on all of the available evidence has led more recently to synthesis methods that address multiple interventions. These methods are commonly referred to as *network meta-analysis, mixed treatment comparisons meta-analysis,* or *multiple treatments meta-analysis* (6–8). In recent years, there has been a notable increase in the publication of articles using these methods (9). On the basis of our recent overview (10) of reporting challenges in the field, as well as findings from our Delphi exercise involving researchers and journal editors, we believe that reporting guidance for such analyses is sorely needed.

In this article, we describe the process of developing specific advice for the reporting of systematic reviews that incorporate network meta-analyses, and we present the guidance generated from this process.

DEVELOPMENT OF THE PRISMA NETWORK META-ANALYSIS EXTENSION STATEMENT

We followed an established approach for this work (11). We formed a steering committee (consisting of Drs. Hutton, Salanti, Moher, Caldwell, Chaimani, Schmid, Thorlund, and Altman); garnered input from 17 journal editors, reporting guideline authors, and researchers with extensive experience in systematic reviews and network meta-analysis; and performed an overview of existing reviews of the reporting quality of network meta-analyses to identify candidate elements important to report in network meta-analyses (10). We also implemented an online Delphi survey of authors of network meta-analyses in mid-2013 (215 invited; response rate, 114 (53%)) by using Fluid Surveys online software (Fluidware, Ottawa, Ontario, Canada) to deter-

See also:
Editorial comment 797

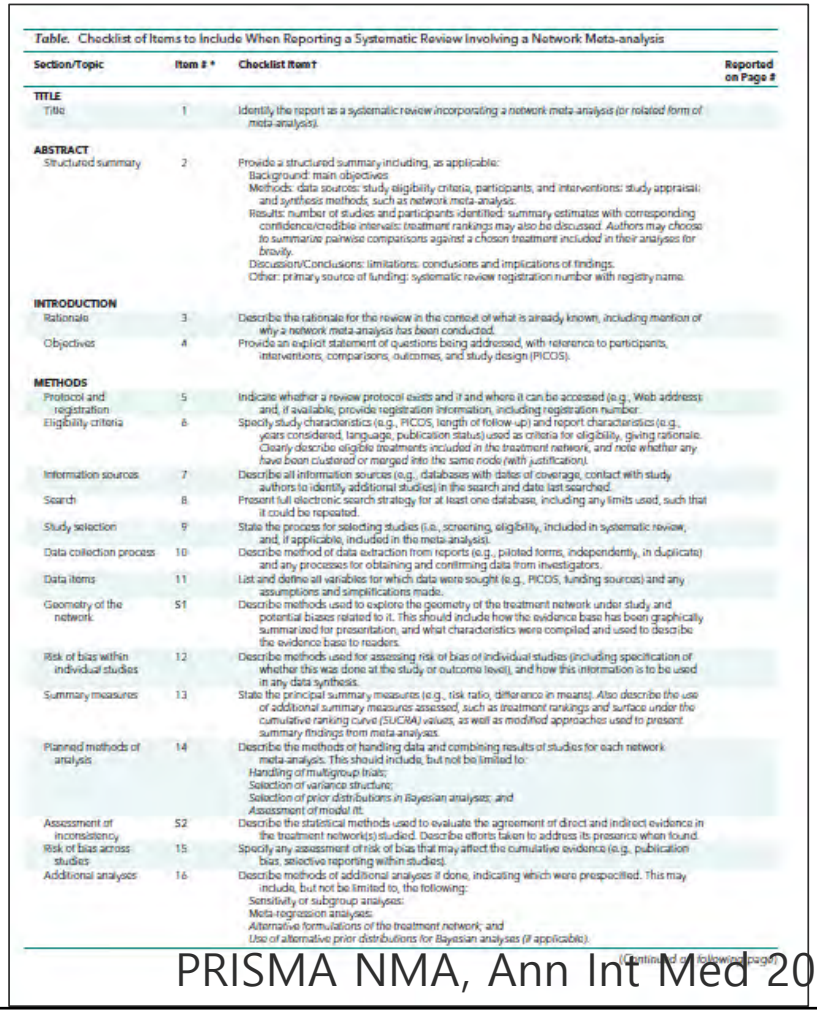


Table. Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis

Section/Topic	Item # *	Checklist Item †	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: Handling of multigroup trials; Selection of variance structure; Selection of prior distributions in Bayesian analyses; and Assessment of model fit.	
Assessment of inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses if done, indicating which were prespecified. This may include, but not be limited to, the following: Sensitivity or subgroup analyses; Meta-regression analyses; Alternative formulations of the treatment network; and Use of alternative prior distributions for Bayesian analyses (if applicable).	

(Continued on following page)

PRISMA NMA, Ann Int Med 2015

まとめ

- 既存のエビデンスからベストの治療を選択するという意味でも適用事例が増えてきている
- 結果の解釈には様々な側面からの検討が必要であり、単純な解釈が難しいことの方が多いことを念頭に置くべき
  - Consistencyの仮定は覚えて帰ってください
- 必ずしも下記の図のように整理はできないことに注意