APPENDIX

Study protocol for systematic review and meta-analysis to determine the comparative effectiveness of various renin-angiotensin system blockers and other antihypertensive drugs in diabetic patients

Objective

To evaluate the effects of different classes of renin-angiotensin system blockers and other antihypertensive treatments, including monotherapy and combination therapy, on survival and major renal outcomes in diabetic patients, by incorporating evidence of direct comparisons with indirect evidence in Bayesian network meta-analysis.

Inclusion Criteria

Study type

- Randomised, parallel-group design clinical trials will be eligible to enter our meta-analysis. Studies with cross-over design will not be eligible.
- We will include studies comparing the effects of any single or combination of antihypertensive drugs with placebo or other classes of active treatments in diabetic patients with a follow-up of at least 12 months.
- We will include studies with two or more than two treatment arms.

Participants

- Eligible Studies should have included diabetic patients older than 18 years.
- We will include studies in patients with any type of diabetes.
- We will include studies in patients with any level of albuminuria.

Outcome measures

- Eligible studies should have reported at least one of the following outcomes: incidence of all-cause death, end-stage renal disease (ESRD), or doubling of serum creatinine.
- ESRD is defined as the need for dialysis therapy or kidney transplantation.
- Eligible studies should have reported the numbers of included participants of each treatment arm.
- Eligible studies should have reported the outcomes of each treatment arm in patient numbers.

Publication type

- Full-length articles or letters in peer-reviewed journals will be eligible.

- No language restrictions will be applied.

Data extraction

The following information will be extracted and entered into databases by two investigators independently (Hon-Yen Wu, Jenq-Wen Huang): study design, patients' characteristics (age, gender, type of diabetes, cardiovascular diseases, baseline and change in blood pressure, and level of albuminuria), interventions, comparisons, and outcomes (all-cause mortality, ESRD, and doubling of serum creatinine). When relevant information regarding design or outcomes is unclear, or when doubt exists for duplicate publications, the original authors will be contacted for clarifications. Disagreements between the two authors will be resolved by discussion. If the disagreement persists, two other senior investigators (Kuan-Yu Hung, Kwan-Dun Wu) will be consulted to attain consensus.

Quality Assessment

The methodological quality of eligible trials will be evaluated independently by two investigators (Hon-Yen Wu, Jenq-Wen Huang) using "the Cochrane Collaboration's tool for assessing risk of bias" (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias).[1] Disagreements between the two authors will be resolved by discussion. If the disagreement persists, two other senior investigators (Kuan-Yu Hung, Kwan-Dun Wu) will be consulted to attain consensus.

Data Synthesis and Analysis

All data from each eligible study will be extracted and entered into a standardised spreadsheet software (Microsoft Excel 2007; Microsoft Corp, Redmond, WA, USA). We will analyse three treatment outcomes separately (all-cause death, ESRD, and doubling of serum creatinine).

Traditional pair-wise meta-analysis will be performed by using Stata software (version 10.0, StataCorp LP, College Station, TX, USA). The pooled estimates of odds ratios and 95% confidence intervals of direct comparisons between two strategies will be calculated using the method of DerSimonian and Laird random-effects model.[1] Heterogeneity of treatment effects across studies will be assessed by I^2 and the Cochrane Q-test.[1] Publication bias will be examined with the funnel plot method, the Begg's adjusted rank correlation test, and the Egger's regression asymmetry test.[2 3]

Network meta-analysis will be performed using the Bayesian hierarchical random-effects model proposed by Lu and Ades.[4] We will use software package WinBUGS (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) to perform network meta-analysis, with random effects models for multi-arm trials developed by Professor Ades and his colleagues (Multi-Parameter Evidence Synthesis Research Group, University of Bristol, Bristol, UK; http://www.bris.ac.uk/cobm/research/mpes/mtc.html). The pooled estimates will be obtained by using the Markov Chains Monte Carlo method (MCMC).
Non-informative priors with vague normal (mean 0, variance 10000) and uniform (0-2) prior distributions will be used for parameters such as means and standard deviations, respectively.[4] The impact of different choices of prior distribution will be examined in sensitivity analyses. For each model, 100000 simulations will be generated for each of the two sets of different initial values, and the first 50000 simulations will be discarded as burn-in period. The achievement of convergence will be assessed using the Brooks-Gelman-Rubin statistic.[5] The median of the posterior distribution based on 100000 simulations will be reported as the point estimate, and the corresponding 95% credible intervals (CrIs) will be obtained using the 2.5th and 97.5th percentiles of the posterior distribution. The inconsistency of the model will be calculated using the node-splitting method, which separates evidence on a particular comparison into direct and indirect evidence.[6 7] The agreement between the direct and indirect evidence will be evaluated, and its Bayesian *P*-value will be reported.[7] Sensitivity analyses will be undertaken by the same methods, after omission of data from specific studies (studies with few patient numbers and events in a specific treatment arm, and studies with a large population that may dominate the data of specific treatment arms). The treatments will be ranked for each outcome in each simulation on the basis of their posterior probabilities. We will assess the probability that each treatment being the most effective therapy, the second best, and so on, by counting the proportion of simulations in which each treatment has the smallest OR, the second smallest, and so on. All results will be reported as odds ratios with corresponding 95% CrIs, as well as the probabilities of ranking by treatment.

Search Strategies

We will search the following electronic databases:

- Medline
- PubMed
- Scopus
- Cochrane Library

There will be no restriction on language of publication.

We will search additional studies in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews.

Medline: Searching using the Ovid interface for the period 1970 to December 2011.

(1) exp Angiotensin-Converting Enzyme Inhibitors/; (2) exp Captopril/; (3) Zofenopril.mp.; (4) exp Enalapril/; (5) exp Ramipril/; (6) Quinapril.mp.; (7) exp Perindopril/; (8) exp Lisinopril/; (9) exp Benzazepines/; (10) exp Fosinopril/; (11) Alacepril.mp.; (12) exp Cilazapril/; (13) Delapril.mp.; (14) Imidapril.mp.; (15) Moexipril.mp.; (16) Rentiapril.mp.; (17) Spirapril.mp.; (18) Temocapril.mp.; (19) Trandolapril.mp.; (20) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19; (21) exp Angiotensin Receptor Antagonists/; (22) Azilsartan.mp.; (23) Candesartan.mp.; (24) Eprosartan.mp.; (25) Irbesartan.mp.; (26) exp Losartan/; (27) Olmesartan.mp.; (28) Tasosartan.mp.; (29) Telmisartan.mp.; (30) Valsartan.mp.; (31) 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30; (32) exp Calcium Channel Blockers/; (33) exp Amlodipine/; (34) Aranidipine.mp.; (35) Azelnidipine.mp.; (36) Barnidipine.mp.; (37) Benidipine.mp.; (38) Cilnidipine.mp.; (39) Clevidipine.mp.; (40) Darodipine.mp.; (41) Efonidipine.mp.; (42) exp Felodipine/; (43) exp Isradipine/; (44) Lacidipine.mp.; (45) Manidipine.mp.; (46) Lercanidipine.mp.; (47) Mepirodipine.mp.; (48) exp Nicardipine/; (49) exp Nifedipine/; (50) Niludipin.mp.; (51) Nilvadipine.mp.; (52) exp Nimodipine/; (53) exp Nisoldipine/; (54) exp Nitrendipine/; (55) Oxodipine.mp.; (56) Pranidipine.mp.; (57) Ryodipine.mp.; (58) Anipamil.mp.; (59) Devapamil.mp.; (60) Emopamil.mp.; (61) Falipamil.mp.; (62) exp Gallopamil/; (63) exp Verapamil/; (64) Clentiazem.mp.; (65) exp Diltiazem/; (66) exp Dihydropyridines/; (67) 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66; (68) exp Adrenergic beta-Antagonists/; (69) exp Alprenolol/; (70) Bopindolol.mp.; (71) exp Bupranolol/; (72) exp Carteolol/; (73) Cloranolol.mp.; (74) Mepindolol.mp.; (75) exp Nadolol/; (76) exp Oxprenolol/; (77) exp Penbutolol/; (78) exp Pindolol/; (79) exp Propranolol/; (80) exp Sotalol/; (81) Tertatolol.mp.; (82) exp Timolol/; (83) exp Betaxolol/; (84) exp Acebutolol/; (85) Bevantolol.mp.; (86) exp Bisoprolol/; (87) Epanolol.mp.; (88) exp Celiprolol/; (89) Esmolol.mp.; (90) exp Metoprolol/; (91) exp Practolol/; (92) exp Atenolol/; (93) Talinolol.mp.; (94) Carvedilol.mp.; (95) exp Labetalol/; (96) Nebivolol.mp.; (97) exp Butoxamine/; (98) 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97; (99) exp Acetazolamide/; (100) exp Diuretics/; (101) exp Furosemide/; (102) exp Bumetanide/;

(103) Torasemide.mp.; (104) exp Ethacrynic Acid/; (105) exp Thiazides/; (106) exp Hydrochlorothiazide/; (107) exp Bendroflumethiazide/; (108) exp Hydroflumethiazide/; (109) exp Chlorothiazide/; (110) exp Polythiazide/; (111) exp Trichlormethiazide/; (112) exp Cyclopenthiazide/; (113) exp Methyclothiazide/; (114) Cyclothiazide.mp.; (115) Mebutizide.mp.; (116) Quinethazone.mp.; (117) exp Clopamide/; (118) exp Chlorthalidone/; (119) exp Mefruside/; (120) Clofenamide.mp.; (121) exp Metolazone/; (122) Meticrane.mp.; (123) exp Xipamide/; (124) exp Indapamide/; (125) Clorexolone.mp.; (126) Fenquizone.mp.; (127) exp Amiloride/; (128) exp Triamterene/; (129) Benzamil.mp.; (130) exp Spironolactone/; (131) Eplerenone.mp.; (132) exp Canrenoate Potassium/; (133) exp Canrenone/; (134) 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133; (135) exp Adrenergic alpha-Antagonists/; (136) exp Prazosin/; (137) exp Indoramin/; (138) Trimazosin.mp.; (139) exp Doxazosin/; (140) Urapidil.mp.; (141) Alfuzosin.mp.; (142) Silodosin.mp.; (143) Tamsulosin.mp.; (144) Terazosin.mp.; (145) 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144; (146) exp Antihypertensive Agents/; (147) 20 or 31 or 67 or 98 or 134 or 145 or 146; (148) Diabetes Mellitus/; (149) Diabetic Nephropathies/; (150) Albuminuria/; (151) 148 or 149 or 150; (152) 147 and 151; (153) limit 152 to (humans and randomized controlled trial).

PubMed: Searching using the NCBI interface for the period 1970 to December 2011.

((angiotensin-converting enzyme inhibitors OR captopril OR zofenopril OR enalapril OR ramipril OR quinapril OR perindopril OR lisinopril OR benzazepines OR fosinopril OR alacepril OR cilazapril OR delapril OR imidapril OR moexipril OR rentiapril OR spirapril OR temocapril OR trandolapril) OR (angiotensin receptor antagonists OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR tasosartan OR telmisartan OR valsartan) OR (calcium channel blockers OR amlodipine OR aranidipine OR azelnidipine OR barnidipine OR benidipine OR cilnidipine OR clevidipine OR darodipine OR efonidipine OR felodipine OR isradipine OR lacidipine OR manidipine OR lercanidipine OR mepirodipine OR nicardipine OR nifedipine OR niludipin OR nilvadipine OR nimodipine OR nisoldipine OR nitrendipine OR oxodipine OR pranidipine OR ryodipine OR anipamil OR devapamil OR emopamil OR falipamil OR gallopamil OR verapamil OR clentiazem OR diltiazem OR dihydropyridines) OR (adrenergic beta-antagonists OR alprenolol OR bopindolol OR bupranolol OR carteolol OR

cloranolol OR mepindolol OR nadolol OR oxprenolol OR penbutolol OR pindolol OR propranolol OR sotalol OR tertatolol OR timolol OR betaxolol OR acebutolol OR bevantolol OR bisoprolol OR epanolol OR celiprolol OR esmolol OR metoprolol OR practolol OR atenolol OR talinolol OR carvedilol OR labetalol OR nebivolol OR butoxamine) OR (acetazolamide OR diuretics OR furosemide OR bumetanide OR torasemide OR ethacrynic acid OR thiazides OR hydrochlorothiazide bendroflumethiazide OR hydroflumethiazide OR chlorothiazide OR polythiazide OR trichlormethiazide OR cyclopenthiazide OR methyclothiazide OR cyclothiazide OR mebutizide OR quinethazone OR clopamide OR chlorthalidone OR mefruside OR clofexamide OR metolazone OR meticrane OR xipamide OR indapamide OR clorexolone OR fenquizone OR amiloride OR triamterene OR benzamil OR spironolactone OR eplerenone OR canrenoate potassium OR canrenone) OR (adrenergic alpha-antagonists OR prazosin OR indoramin OR trimazosin OR doxazosin OR urapidil OR alfuzosin OR silodosin OR tamsulosin OR terazosin) OR (antihypertensive agents)) AND (diabetes mellitus OR diabetic nephropathies OR albuminuria) AND (Humans[Mesh])

Scopus: Searching using the Elsevier interface for the period 1970 to December 2011.

(((ALL("randomized controlled trial" .pt) OR ALL((random$ OR placebo$ OR single blind$ OR double blind$ OR triple blind$) .ti,ab) OR ALL((retraction of publication OR retracted publication) .pt))) AND NOT ((ALL((animals not humans) .sh) OR ALL(((comment OR editorial OR meta-analysis OR practice-guideline OR review OR letter OR journal correspondence) not "randomized controlled trial") .pt) OR ALL((random sampl$ OR random digit$ OR random effect$ OR random survey OR random regression) .ti,ab. not "randomized controlled trial" .pt)))) AND (((angiotensin-converting enzyme inhibitors OR captopril OR zofenopril OR enalapril OR ramipril OR quinapril OR perindopril OR lisinopril OR benzazepines OR fosinopril OR alacepril OR cilazapril OR delapril OR imidapril OR moexipril OR rentiapril OR spirapril OR temocapril OR trandolapril) OR (angiotensin receptor antagonists OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR tasosartan OR telmisartan OR valsartan) OR (calcium channel blockers OR amlodipine OR aranidipine OR azelnidipine OR barnidipine OR benidipine OR cilnidipine OR clevidipine OR darodipine OR efonidipine OR felodipine OR isradipine OR lacidipine OR manidipine OR lercanidipine OR mepirodipine OR nicardipine OR nifedipine OR niludipin OR nilvadipine OR nimodipine OR nisoldipine OR nitrendipine OR oxodipine OR pranidipine OR

ryodipine OR anipamil OR devapamil OR emopamil OR falipamil OR gallopamil OR verapamil OR clentiazem OR diltiazem OR dihydropyridines) OR (adrenergic beta-antagonists OR alprenolol OR bopindolol OR bupranolol OR carteolol OR cloranolol OR mepindolol OR nadolol OR oxprenolol OR penbutolol OR pindolol OR propranolol OR sotalol OR tertatolol OR timolol OR betaxolol OR acebutolol OR bevantolol OR bisoprolol OR epanolol OR celiprolol OR esmolol OR metoprolol OR practolol OR atenolol OR talinolol OR carvedilol OR labetalol OR nebivolol OR butoxamine) OR (acetazolamide OR diuretics OR furosemide OR bumetanide OR torasemide OR ethacrynic acid OR thiazides OR hydrochlorothiazide bendroflumethiazide OR hydroflumethiazide OR chlorothiazide OR polythiazide OR trichlormethiazide OR cyclopenthiazide OR methyclothiazide OR cyclothiazide OR mebutizide OR quinethazone OR clopamide OR chlorthalidone OR mefruside OR clofexamide OR metolazone OR meticrane OR xipamide OR indapamide OR clorexolone OR fenquizone OR amiloride OR triamterene OR benzamil OR spironolactone OR eplerenone OR canrenoate potassium OR canrenone) OR (adrenergic alpha-antagonists OR prazosin OR indoramin OR trimazosin OR doxazosin OR urapidil OR alfuzosin OR silodosin OR tamsulosin OR terazosin) OR (antihypertensive agents)) AND (diabetes mellitus OR diabetic nephropathies OR albuminuria))

Cochrane Library: Searching using the Wiley interface for the period 1970 to December 2011.

(1) Angiotensin-Converting Enzyme Inhibitors OR Captopril OR Zofenopril OR Enalapril OR Ramipril OR Quinapril OR Perindopril OR Lisinopril OR Benzazepines OR Fosinopril OR Alacepril OR Cilazapril OR Delapril OR Imidapril OR Moexipril OR Rentiapril OR Spirapril OR Temocapril OR Trandolapril; (2) Angiotensin Receptor Antagonists OR Azilsartan OR Candesartan OR Eprosartan OR Irbesartan OR Losartan OR Olmesartan OR Tasosartan OR Telmisartan OR Valsartan; (3) Calcium Channel Blockers OR Amlodipine OR Aranidipine OR Azelnidipine OR Barnidipine OR Benidipine OR Cilnidipine OR Clevidipine OR Darodipine OR Efonidipine OR Felodipine OR Isradipine OR Lacidipine OR Manidipine OR Lercanidipine OR Mepirodipine OR Nicardipine OR Nifedipine OR Niludipin OR Nilvadipine OR Nimodipine OR Nisoldipine OR Nitrendipine OR Oxodipine OR Pranidipine OR Ryodipine OR Anipamil OR Devapamil OR Emopamil OR Falipamil OR Gallopamil OR Verapamil OR Clentiazem OR Diltiazem OR Dihydropyridines; (4) Adrenergic beta-Antagonists OR Alprenolol OR Bopindolol OR Bupranolol OR

Carteolol OR Cloranolol OR Mepindolol OR Nadolol OR Oxprenolol OR Penbutolol OR Pindolol OR Propranolol OR Sotalol OR Tertatolol OR Timolol OR Betaxolol OR Acebutolol OR Bevantolol OR Bisoprolol OR Epanolol OR Celiprolol OR Esmolol OR Metoprolol OR Practolol OR Atenolol OR Talinolol OR Carvedilol OR Labetalol OR Nebivolol OR Butoxamine; (5) Acetazolamide OR Diuretics OR Furosemide OR Bumetanide OR Torasemide OR Ethacrynic Acid OR Thiazides OR Hydrochlorothiazide Bendroflumethiazide OR Hydroflumethiazide OR Chlorothiazide OR Polythiazide OR Trichlormethiazide OR Cyclopenthiazide OR Methyclothiazide OR Cyclothiazide OR Mebutizide OR Quinethazone OR Clopamide OR Chlorthalidone OR Mefruside OR Clofenamide OR Metolazone OR Meticrane OR Xipamide OR Indapamide OR Clorexolone OR Fenquizone OR Amiloride OR Triamterene OR Benzamil OR Spironolactone OR Eplerenone OR Canrenoate Potassium OR Canrenone; (6) Adrenergic alpha-Antagonists OR Prazosin OR Indoramin OR Trimazosin OR Doxazosin OR Urapidil OR Alfuzosin OR Silodosin OR Tamsulosin OR Terazosin; (7) Antihypertensive Agents; (8) (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7); (9) Diabetes Mellitus OR Diabetic Nephropathies OR Albuminuria; (10) (#8 AND #9); (11) (#10), from 1970 to 2011.

Limits: publication type as journal.

References

1. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration, 2011*; Available from www.cochrane-handbook.org. Accessed Oct 1, 2011.
2. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088-101.
3. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-34.
4. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; 23: 3105-24.
5. Brooks SP, Gelman A. Alternative methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998; 7: 434-45.
6. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *J Am Stat Assoc* 2006; 101: 477-59.
7. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010; 29: 932-44.