**Supplementary File**

**Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: A rapid evidence assessment of recent literature**

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# Appendix I: Supplementary Tables – Search Strategy

## TABLE S1A. Embase® search and number of hits (1 Jan 2013 to 11 Jan 2019

|  |  |  |
| --- | --- | --- |
|  | Search term | Hits |
| 1 | exp ANTIHYPERTENSIVE AGENTS/ | 646 372 |
| 2 | exp hypertension/ | 659 362 |
| 3 | exp blood pressure/ | 508 957 |
| 4 | (high or elevated or raised or increas\*).mp. | 10 240 130 |
| 5 | 3 and 4 | 288 424 |
| 6 | hypertens\*.tw. | 582 117 |
| 7 | ((high or elevated or raised or increas\*) adj2 (blood pressure orbloodpressure or bp)).mp. (67144) | 67 418 |
| 8 | 1 or 2 or 5 or 6 or 7 | 1 459 531 |
| 9 | exp drug combinations/ | 107 760 |
| 10 | ((single or fixed or bitherap\* or bi-therap\* or therap\* or drug\* or medicat\* or medicin\* or pill\* or (one adj pill) or onepill) adj3 combin\*).mp | 1 026 665 |
| 11 | FDC.ti,ab. | 3446 |
| 12 | SPC.ti,ab. | 5561 |
| 13 | all-in-one.ti,ab. | 1793 |
| 14 | (polypill\* or poly-pill\*).tw. | 541 |
| 15 | ((single adj pill\*) or singlepill\*).tw. | 785 |
| 16 | (co-formulat\* or coformulat\*).mp. | 1358 |
| 17 | (multiingredient\* or multi-ingredient\*).mp. | 227 |
| 18 | ((single or fixed or bitherap\* or bi-therap\*) adj3 (dose\* or dosage\* or preparation\* or formulation\* or mixture\*)).mp. | 184 894 |
| 19 | exp drug therapy combination/ | 167 127 |
| 20 | or/9-19 | 1 239 865 |
| 21 | (benazepril or captopril or enalapril or fosinopril or lisinopril or moexipril or perindopril or quinapril or trandolapril or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan or bisoprolol or metoprolol or nadolol or tenormin or atenolol or amlodipine or azelnidipine or felodipine or verapamil or aliskiren or bendroflumethiazide or chlorthalidone or HCTZ or hydrochlorothiazide or amiloride or spironolactone or triamterene).mp. | 264 502 |
| 22 | \*patient compliance/ | 21 208 |
| 23 | exp compliance/ | 299 233 |
| 24 | \*medication compliance/ | 7342 |
| 25 | complian\*.mp. | 310 489 |
| 26 | exp medication adherence/ | 25 270 |
| 27 | persistence\*.mp. | 104 228 |
| 28 | ((medication\* or drug\* or therap\* or treatment) adj3 (complian\* or adheren\* or persist\*)).mp. | 103 679 |
| 29 | (stay-on adj3 (therap\* or drug\* or medicat\* or treatment)).mp. | 206 |
| 30 | or/22-29 | 443 078 |
| 31 | 8 and 20 and 21 and 29 | 2907 |
| 32 | conference abstract.pt. | 3 255 639 |
| 33 | 30 not 31 | 2718 |
| 34 | limit 32 to english language | 2438 |
| 35 | limit 33 to humans | 2318 |
| 36 | limit 34 to yr="2013 -Current" | 595 |
| Search carried out within “Embase 1974” from 2013 to 11 Jan 2019.  |

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# TABLE S1B. MEDLINE® search and number of hits (1 Jan 2013 to 11 Jan 2019)

|  | **Search term** | **Hits** |
| --- | --- | --- |
| 1 | exp ANTIHYPERTENSIVE AGENTS/ | 246 141 |
| 2 | exp hypertension/ | 242 692 |
| 3 | exp blood pressure/ | 279 309 |
| 4 | (high or elevated or raised or increas\*).mp. | 7 771 015 |
| 5 | 3 and 4 | 137 850 |
| 6 | hypertens\*.tw. | 393 817 |
| 7 | ((high or elevated or raised or increas\*) adj2 (blood pressure or bloodpressure or bp)).mp. | 47 626 |
| 8 | 1 or 2 or 5 or 6 or 7 | 711 383 |
| 9 | exp drug combinations/ | 84 286 |
| 10 | ((single or fixed or bitherap\* or bi-therap\* or therap\* or drug\* or medicat\* or medicin\* or pill\* or (one adj pill) or onepill) adj3 combin\*).mp. | 490 108 |
| 11 | FDC.ti,ab. | 2385 |
| 12 | SPC.ti,ab. | 3797 |
| 13 | all-in-one.ti,ab. | 1428 |
| 14 | (polypill\* or poly-pill\*).tw. | 384 |
| 15 | ((single adj pill\*) or singlepill\*).tw. | 494 |
| 16 | (co-formulat\* or coformulat\*).mp. | 864 |
| 17 | (multiingredient\* or multi-ingredient\*).mp. | 218 |
| 18 | ((single or fixed or bitherap\* or bi-therap\*) adj3 (dose\* or dosage\* or preparation\* or formulation\* or mixture\*)).mp. | 104 876 |
| 19 | exp drug therapy combination/ | 306 287 |
| 20 | or/9-19 | 7 066 122 |
| 21 | (benazepril or captopril or enalapril or fosinopril or lisinopril or moexipril or perindopril or quinapril or trandolapril or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan or bisoprolol or metoprolol or nadolol or tenormin or atenolol or amlodipine or azelnidipine or felodipine or verapamil or aliskiren or bendroflumethiazide or chlorthalidone or HCTZ or hydrochlorothiazide or amiloride or spironolactone or triamterene).mp. | 111 102 |
| 22 | \*patient compliance/ | 23 137 |
| 23 | exp compliance/ | 3918 |
| 24 | complian\*.mp. | 160 089 |
| 25 | exp medication compliance/ | 9701 |
| 26 | exp medication adherence/ | 15 673 |
| 27 | Persistence\*.mp. | 80 795 |
| 28 | ((medication\* or drug\* or therap\* or treatment) adj3 (complian\* or adheren\* or persist\*)).mp. | 61 815 |
| 29 | (stay-on adj3 (therap\* or drug\* or medicat\* or treatment)).mp. | 92 |
| 30 | or/22-29 | 275 149 |
| 31 | 8 and 20 and 21 and 28 | 599 |
| 322 | limit 29 to english language | 497 |
| 33 | limit 30 to humans | 439 |
| 32 | limit 31 to yr="2013 -Current" | 110 |
| Search carried out in Ovid MEDLINE® and In-process & other Non-Indexed citations 1946 to 11 Jan 2019. |

## TABLE S1C. Cochrane® search and number of hits 2013 to present: Data capture 14 Jan 2019

|  | **Search term** | **Hits** |
| --- | --- | --- |
| 1 | exp ANTIHYPERTENSIVE AGENTS/ | 25 187 |
| 2 | exp hypertension/ | 16 387 |
| 3 | exp blood pressure/ | 26 350 |
| 4 | (high or elevated or raised or increas\*).mp. | 461 180 |
| 5 | 3 and 4 | 14 973 |
| 6 | hypertens\*.tw. | 44 956 |
| 7 | ((high or elevated or raised or increas\*) adj2 (blood pressure or bloodpressure or bp)).mp. | 7675 |
| 8 | 1 or 2 or 5 or 6 or 7 | 71 345 |
| 9 | exp drug combinations/ | 7675 |
| 10 | ((single or fixed or bitherap\* or bi-therap\* or therap\* or drug\* or medicat\* or medicin\* or pill\* or (one adj pill) or onepill) adj3 combin\*).mp. | 1 111 135 |
| 11 | FDC.ti,ab. | 654 |
| 12 | SPC.ti,ab. | 218 |
| 13 | all-in-one.ti,ab. | 261 485 |
| 14 | (polypill\* or poly-pill\*).tw. | 88 |
| 15 | ((single adj pill\*) or singlepill\*).tw. | 204 |
| 16 | (co-formulat\* or coformulat\*).mp. | 296 |
| 17 | (multiingredient\* or multi-ingredient\*).mp. | 60 |
| 18 | ((single or fixed or bitherap\* or bi-therap\*) adj3 (dose\* or dosage\* or preparation\* or formulation\* or mixture\*)).mp. | 47 593 |
| 19 | exp drug therapy combination/ | 41 702 |
| 20 | or/9-19 | 387 648 |
| 21 | (benazepril or captopril or enalapril or fosinopril or lisinopril or moexipril or perindopril or quinapril or trandolapril or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan or bisoprolol or metoprolol or nadolol or tenormin or atenolol or amlodipine or azelnidipine or felodipine or verapamil or aliskiren or bendroflumethiazide or chlorthalidone or HCTZ or hydrochlorothiazide or amiloride or spironolactone or triamterene).mp. | 25 410 |
| 22 | \*patient compliance/ | 0 |
| 23 | exp compliance/ | 222 |
| 24 | complian\*.mp. | 38 406 |
| 25 | exp medication adherence/ | 1841 |
| 26 | Persistence\*.mp. | 4017 |
| 27 | ((medication\* or drug\* or therap\* or treatment) adj3 (complian\* or adheren\* or persist\*)).mp. | 20 931 |
| 28 | (stay-on adj3 (therap\* or drug\* or medicat\* or treatment)).mp. | 1487 |
| 29 | or/22-28 | 52 178 |
| 30 | 8 and 20 and 21 and 28 | 482 |
| 31 | limit 29 to english language [Limit not valid in CDSR; records were retained] | 482 |
| 32 | limit 30 to humans [Limit not valid in CCTR,CDSR; records were retained] | 482 |
| 33 | limit 31 to yr="(2013)(2009)(2003) -Current" | 157 |
| 34 | Conference abstract.pt | 48 683 |
| 35 | 33 not 34 | 165 |
| 36 | remove duplicates from 34 | 156 |
| Search carried out within EMB Reviews - Cochrane Central Register of Controlled Trials December 2018, EMB Reviews - Cochrane Database of Systematic Reviews 2005 to 11 Jan 2019. |

## TABLE S2. Therapeutic agents listed as search terms to be available within the combination therapy

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ACEi | ARB | BB | CCB | DRI | Diuretic | K+ sparing diuretic |
| benazepril | azilsartan | bisoprolol | amlodipine | aliskiren | bendroflume-thiazide | amiloride |
| captopril | candesartan | metoprolol | azelnidipine |  | chlorthalidone | spironolactone |
| enalapril | eprosartan | nadolol | felodipine |  | hydrochlorothiazideOr HCTZ  | triamterene |
| fosinopril | irbesartan | atenolol | verapamil |  |  |
| lisinopril | losartan |  |  |  |  |  |
| moexipril | olmesartan |  |  |  |  |  |
| perindopril | telmisartan |  |  |  |  |  |
| quinapril | valsartan |  |  |  |  |  |
| trandolapril | fimasartan |  |  |  |  |  |
| ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; DRI, direct renin inhibitor; HCTZ, hydrochlorothiazide. |

# Appendix II: Supplementary Tables – Additional Results

## TABLE S3. Summary of study characteristics in 29 articles identified in the rapid evidence assessment of recent literature

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author, year | Country | Publication type | Sample size | Age (mean or median) , % male  | SPC or free combination | Intervention(s) and Dose (mg) | Primary observation | Secondary observations  |
| Kumagai N, 2013 [[1](#_ENREF_1)] | Japan | Observational retrospective | 196 | 69, 57.0 | SPC | ARB/amlo (ARB; cand 8 mg, tel 40 mg, amlo 5) | Change in mean home BP, drug adherence and healthcare costs |  |
| Panjabi S, 2013 [[2](#_ENREF_2)] | USA | Observational retrospective | 1335 | 58.2, 50.2 | Free | amlo + HCTZ + ARB | Adherence and persistence. Treatment modification. Healthcare cost and resource utilization. CV and renal outcomes | Treatment modification. Healthcare cost and resource utilization. CV and renal outcomes |
| 4005 | 58.8, 50.5 | SPC | amlo/ARB + HCTZ or ARB/HCTZ + amlo |  |
| 3041 | 56.8, 56.0 | Free | amlo + HCTZ + ACEi |
| 6082 | 57.6, 54.7 | SPC | amlo/ACEi + HCTZ or ACEi/HCTZ + amlo |
| 1218 | 59.8, 41.8 | Free | amlo + HCTZ + BB |
| 609 | 60.3, 41.2 | SPC | BB/HCTZ + amlo |
| Bramlage P, 2014 [[3](#_ENREF_3)] | Multi-national (Europe) | Observational prospective | 14 979 | 63.9, 53.5 | SPC | olm/amlo/HCTZ(20/5/12.5, 40/5/12.5, 40/5/25, 40/10/12.5 or 40/10/25) | BP lowering efficacy, safety and tolerability | Patient adherence |
| Degli Esposti L, 2014 [[4](#_ENREF_4)] | Italy | Observational retrospective | 239 | 64.4, 53.4  | SPC | Olm/amlo | Criteria for prescribing an FDC pill. Patient adherence |  |
| 20 769 | 64.8, 50.4  | Free | Other antihypertensive  |
| Jadhav U, 2014 [[5](#_ENREF_5)] | India | Observational prospective | 196 | 52.3, 49.0 | SPC | ind/amlo (1.5/5) | Mean change in BP from baseline to end | Patients achieving BP control, safety and tolerability |
| Xie L, 2014 [[6](#_ENREF_6)] | USA | Observational retrospective | 8516 | 54.83, 54.77 | SPC | olm/amlo/HCTZ or val/amlo/HCTZ | Patient adherence and persistence |  |
| 7842 | 59.08, 50.55%  | Mix (2 pills, 1 SPC) | olm/amlo + HCTZ or val/amlo + HCTZ, or olm/HCTZ + amlo, or val/HCTZ + amlo  |
| 1107 | 63.88, 48.69  | Free | olm + almo + HCTZ or val + almo + HCTZ |
| Czarnecka D, 2015 [[7](#_ENREF_7)] | Poland | Observational prospective | 4288 | 59.3, 50.3 | SPC | bis/amlo(5/5, 10/5, 5/10, 10/10) | Patient adherence | Change in blood pressure from baseline and after 6 mo |
| Hsu CI, 2015 [[8](#_ENREF_8)] | Taiwan | Observational prospective | 5725 | 55.0, 55.9 | SPC | ARB/thiazide diuretic | Patient adherence and persistence |  |
| 1623 | 55.9, 54.4 | Free | ARB + thiazide diuretic |
| Jung H-W, 2015 [[9](#_ENREF_9)] | Korea | Observational prospective | 110 (untreated) | 48.0, 68.2 | SPC | olm/amlo (20/5, 40/5, 40/10) | Mean change in seated DBP | Changes in BP from baseline to wk 4, 8 and 12, achieving target BP. Changes in 24 h ambulatory BP from baseline to wk 12 |
| 132 (nonresponder to amlo) | 55.2, 57.6 | SPC | olm/amlo (20/5, 40/5, 40/10) |
| 134 (nonresponder to los) | 53.2, 54.5 | SPC | olm/amlo (20/5, 40/5, 40/10) |
| Machnicki G, 2015 [[10](#_ENREF_10)] | USA | Observational retrospective | 1884 | 66.4, 51.6 | SPC  | amlo/val/HCTZ | Patient adherence | Patient persistence. All-cause and hypertension-specific healthcare utilization and costs (at 12 mo) |
| 1884 | 66.8, 52.0 | Free | amlo + val + HCTZ |
| Mancia G, 2015 [[11](#_ENREF_11)] | Multi-national(Europe) | RCT | 888 | 55.7, 54.0 | SPC | per/amlo (3.5/2.5, 7/5, 14/10) | Change in SBP between baseline and 3 mo | Change in SBP and DBP from baseline. Rates of BP control and up-titration. Change in SBP and DBP in subgroups (sex, age, presence of diabetes mellitus, grade of hypertension at baseline) |
| 886 | 55.2, 53.0 | SPC | val/amlo (160/5, 160/10 |
| Manolis A, 2015 [[12](#_ENREF_12)] | Greece | Observational prospective | 2300 | 64.3, 53.3 | SPC | per/amlo (5/5, 5/10, 10/5, 10/10) | Mean SBP and DBP reduction over 6 mo. BP control after 6 mo | Patient compliance. Identification of total CV risk and coexisting risk factors of patients  |
| Rosenkranz AR, 2015 [[13](#_ENREF_13)] | Austria | Observational prospective | 566 | 63.8, 53.5 | SPC | ali/amlo (150/5, 150/10, 300/5, 300/10) | Efficacy, tolerability and patient adherence over 3 mo |  |
| Setiawati A, 2015 [[14](#_ENREF_14)] | Indonesia | Observational prospective | 500 | 55.8, 54.6 | SPC | amlo/val (5/80, 5/160, 10/160) | Change in mean sitting SBP and DBP from baseline to wk 26. Achievement of BP goal. Patient responders | Safety and tolerability |
| Tung Y-C, 2015 [[15](#_ENREF_15)] | Taiwan | Observational retrospective | 3301 | 60.30, 52.2 | SPC | amlo/val | Clinical outcomes and healthcare costs of FDC vs. free | Adherence and persistence |
| 13 204 | 60.37, 51.2 (13.09) | Free | ARB + CCB |
| Assaad-Khalil SH, 2016 [[16](#_ENREF_16)] | Egypt | Observational prospective | 2566 | 52.6, 60.9 | SPC | amlo/val(5/160 or 10/160) | Change in msSBP and msDBP from baseline to end of study | Achievement of therapeutic BP goal and BP response |
| Levi M, 2016 [[17](#_ENREF_17)] | Italy | Observational retrospective | 4522 | 66.6 47.8 | SPC | olm/amlo (20/5 mg, 40/10 mg, or 40/5) | Patient adherence (after 6 mo) |  |
| 2090 | 68.1, 49.2 | Free | olm + amlo |
| Simonyi G, 2016 [[18](#_ENREF_18)] | Hungary | Observational retrospective | 10 295 | NR | SPC | ram/amlo | Patient adherence |  |
| 28 800 | NR | SPC | ram/HCTZ |
| Vlachopoulos C, 2016 [[19](#_ENREF_19)] | Greece | Observational prospective | 2269 | 65.3, 52.4 | SPC | per/amlo (5/5, 5/10, 10/5, 10/10) | Patient adherence over 4 mo | Change in BP. BP control. CV risk. Comorbidities. Coexisting risk factors |
| Lauffenburger JC, 2017 [[20](#_ENREF_20)] | USA | Observational retrospective | 78 958 | 49.3, 48.0 | SPC | NR | Persistence to any antihypertensive medication 12 mo after initiation | Adherence to at least 1 antihypertensive 12 mo after initiation. Refilling at least 1 antihypertensive medication |
| 383 269 | 46.8, 48.3 | Single therapy(1 pill) | NR |
| 22 266 | 52.5, 63.6 | Free combination | NR |
| Liakos CI, 2017 [[21](#_ENREF_21)] | Greece | Observational prospective | 1907 | 65.2, 59.1 | SPC | per/amlo (5/5, 5/10, 10/5, 10/10) | Patient adherence | Safety and tolerance. Change in office BP (SBP and DBP) and change in BMI (over 4 mo) |
| Mourad J-J, 2017 [[22](#_ENREF_22)] | Multi-national  | RCT | 227 | 54.5, 61.2 | SPC | per/ind/amlo (5/1.25/5, 5/1.25/10, 10/2.5/5, 10/2.5/10) | Change in BP of FDC triple therapy vs. double therapy | Change in supine BP. Rates of controlled BP. Response to treatment. Standing SBP and DBP |
| 227 | 54.9, 49.8  | SPC | per/ind (5/1.25) |
| Nedogoda SV, 2017 [[23](#_ENREF_23)] | Multi-national | RCT | 75 | 57.2, 46.7 | SPC | per/ind/amlo (5/1.25/5) | Change in office supine SBP and DBP from baseline over 12 wks | Change in office supine SBP and DBP from baseline over wks 0–4 and 0–8. BP control. Tolerability and safety |
| 73 | 55.6, 47.9 | Free | per/ind + amlo (5/1.25 + 5) |
| Simons LA, 2017 [[24](#_ENREF_24)] | Australia | Observational retrospective | 9340 | 67.8, 49.0%  | SPC | amlo/per | Patient adherence and mortality |  |
| 3093 | 71.5, 46.0  | Free | amlo + per |
| Bramlage P, 2018 [[25](#_ENREF_25)] | Germany | Observational retrospective | 10 938 | 63.4, 56.2 | SPC | ram/amlo | Comorbidities and factors associated with prescription of an FDC rather than a free combination | Persistence and adherence, change in BP, treatment costs |
| 60 525 | 68.9, 49.9 | Free | ram + amlo |
| 1413 | 64. , 49.5 | SPC | cand/amlo |
| 9082 | 70.0, 43.8 | Free | cand + amlo |
| Degli Esposti L, 2018 [[26](#_ENREF_26)] | Italy | Observational retrospective | 3597 | NR | SPC | per/amlo | Patient adherence |  |
| 20 423 | NR | Free | Other antihypertensive |
| Fleig SV, 2018 [[27](#_ENREF_27)] | Germany | Observational prospective | 1814 | 60.0, 54  | SPC | per/amlo (3.5/2.5 or 7/5) | Change in office, 24-h ambulatory and home BP from baseline to final visit. Hypertension severity | Patient adherence, safety and tolerability. Adverse events. Adverse drug reactions |
| Verma AA, 2018 [[28](#_ENREF_28)] | Canada | Observational retrospective | 6675 | 71(median), 44.9 | Free | NR | All-cause death and hospitalization for AMI, heart failure or stroke | The individual components of the primary observation. Safety |
| Verma AA, 2018 [12] |  |  | 6675 | 71 (median), 46.2 | SPC | NR |  |  |
| Webster R, 2018 [[29](#_ENREF_29)] | Sri Lanka | RCT | 349 | 56.4, 40.7 | SPC | tel/amlo/chlo (20/2.5/12.5, 40/5/25) | BP control target at 6 mo | Achieving target BP at 6 and 12 wks. Mean SBP and DBP change at 6 mo. Self-reported adherence to BP-lowering medicine. Intolerance of treatment at 6 mo. Frequency of changes in BP-lowering medications |
| 351 | 56.0, 44.2  | Free | NR |
| ACEi, angiotensin-converting enzyme inhibitor; amlo, amlodipine; ARB, angiotensin-receptor blocker; BB, beta-blocker; bis, bisoprolol; BL, baseline; BP, blood pressure; CCB, calcium channel blocker; chlo, chlorthalidone; FDC, fixed-dose combination; HCTZ, hydrochlorothiazide; HTN, hypertensive; ind, indapamide; los, losartan; nRCT, non-randomized control trial; NR, not reported; olm, olmesartan; per, perindopril; ram, ramipril; RCT, randomized clinical trial; SD, standard deviation; tel, telmisartan; val, valsartan. |

## TABLE S4. Summary of serious adverse events

| Author, year | Sample size | Treatment (SPC/free) | Treatment details | SAE*n* (%) | Details |
| --- | --- | --- | --- | --- | --- |
| Fleig SV, 2018 [[27](#_ENREF_27)] | 1814 | SPC | per/amlo | 8 (0.4) | Not reported1 fatal event in a patient with HTN crisis |
| Webster R, 2018 [[29](#_ENREF_29)]  | 349 | SPC | Tel/amlo/chlo | 27 (7.7) | 0 (0.0%) deaths; 1 (0.3%) life-threatening; 26 (7.4%) in-patient hospitalization |
|  | 351 | Free | Not specified | 21 (6.0) | 2 (0.6%) deaths; 0 life-threatening; 19 (5.4%) in-patient hospitalizations  |
| Assaad-Khalil SH, 2016 [[16](#_ENREF_16)] | 2566 | SPC | amlo/val | 12 (0.5) | 2 events, chest tightness on day 8 and renal failure on day 152, suspected to be related to the study drug Most frequent SAE: cardiac disorders (*n*=5; 0.2 %) |
| Czarnecka D, 2015 [[7](#_ENREF_7)] | 4288 | SPC | bis/amlo | 2 (0.5) | 1 case of AF, 1 case of CHF worsening |
| Mancia G, 2015 [[11](#_ENREF_11)] | 888 | SPC | per/amlo | 0 | No treatment-related SAE or relevant changes in laboratory values or vital signs |
|  | 886 | SPC | val/amlo | 0 | No treatment-related SAE or relevant changes in laboratory values or vital signs |
| Manolis A, 2015 [[12](#_ENREF_12)] | 2300 | SPC | per/amlo | 6 (0.2) | 1 case (face oedema) was suspected of being drug-related |
| Setiawati A, 2015 [[14](#_ENREF_14)] | 464 | SPC | amlo/val | 5 (1) | 4 deaths: 1 nonhaemorrhagic stroke on study day 118, and 3 MI on study days 30, 92 and 140; (None of the 4 deaths were suspected to be related to the study drug)1 patient reported nonfatal SAE (dyspnea, insomnia, edema) not related to study drug |
| Bramlage P, 2018 [[25](#_ENREF_25)] | 14 979 | SPC | olm/amlo/HCTZ | 24 (0.16) | Not reported |
| AF, atrial fibrillation; amlo, amlodipine; bis, bisoprolol; CHF, chronic heart failure; chlo, chlorthalidone; HCTZ, hydrochlorothiazide; HTN, hypertension; NR, not reported; olm, olmesartan; per, perindopril; SAE, serious adverse event; tel, telmisartan; val, valsartan. |

## TABLE S5.Methodological reporting assessment according to (A) NICE STA method of scoring RCTs [[30](#_ENREF_30)], and (B) the Newcastle-Ottawa Quality assessment scale method of scoring observational studies [[31](#_ENREF_31)]

|  |
| --- |
| (A) |
| Study (Author, year)  | **Randomization** | **Concealment of allocation** | **Groups similar at baseline** | **Blinded to allocation** | **Drop out imbalance?** | **More outcomes than reported** | **Were the interventions clearly described?** | **Were the eligibility criteria clearly described?** | **Were all potential confounders considered?** | **Were appropriate statistical analysis implemented?** | **ITT** |
|
| Webster R, 2018 [[29](#_ENREF_29)]  | Low | HigH | Low | HigH | Low | Low | Low | Low | Low | Low | Low |
| Mourad JJ, 2017 [[22](#_ENREF_22)] | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Nedogoda, 2017 [[23](#_ENREF_23)] | Low | HigH | Low | HigH | Low | Low | Low | Low | Low | Low | Low |
| Mancia G, 2015 [[11](#_ENREF_11)] | Low | Low | Low | Low | Low | Low | Low | Low | uncLear | Low | Low |
| NICE STA, National Institute of Health and Care Excellence Single Technology Appraisal; ITT, intent-to-treat analysis; RCT, randomized controlled trial. |

|  |
| --- |
| (B)  |
| Study (author, year)  | **Total score**  | **Selection** | **Comparability** | **Outcome** |
| **1 Representativeness of the exposed cohort** | **2 Selection of the non- exposed cohort** | **3Ascertainment of exposure** | **4 Demonstration that outcome of interest was not present at start of study** | **1 Comparability of cohorts on the basis of the design or analysis** | **1Assessment of outcome** | **2Was follow-up long enough for outcomes to occur?** | **3Adequacy of follow-up of cohorts** |
| Assaad-Khalil SH, 2016 [[16](#_ENREF_16)] | 5 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| Bramlage P, 2014 [[3](#_ENREF_3)] | 6 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Bramlage P, 2018 [[25](#_ENREF_25)] | 6 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 |
| Czarnecka D, 2015 [[7](#_ENREF_7)] | 5 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| Degli Esposti L, 2014 [[4](#_ENREF_4)] | 8 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Degli Esposti L, 2018 [[26](#_ENREF_26)] | 8 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Fleig SV, 2018 [[27](#_ENREF_27)] | 8 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Hsu CI, 2015 [[8](#_ENREF_8)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Jadhav U, 2014 [[5](#_ENREF_5)] | 6 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Jung H-W, 2015 [[9](#_ENREF_9)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Kumagai N, 2013 [[1](#_ENREF_1)] | 6 | 1 | 1 | 1 | 1 | 2 | 0 | 0 | 0 |
| Lauffenburger JC, 2017 [[20](#_ENREF_20)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Levi M, 2016 [[17](#_ENREF_17)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Liakos CI, 2017 [[21](#_ENREF_21)] | 6 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Machnicki G, 2015 [[10](#_ENREF_10)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Manolis A, 2015 [[12](#_ENREF_12)] | 6 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Panjabi S 2013 [[2](#_ENREF_2)] | 8 | 1 | 0 | 1 | 1 | 2 | 1 | 1 | 1 |
| Rosenkranz AR, 2015 [[13](#_ENREF_13)] | 6 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Setiawati A, 2015 [[14](#_ENREF_14)] | 5 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| Simons LA, 2017 [[24](#_ENREF_24)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Simonyi G, 2016 [[18](#_ENREF_18)] | 5 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| Tung Y-C, 2015 [[15](#_ENREF_15)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Verma AA, 2018 [[28](#_ENREF_28)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Vlachopoulos C, 2016 [[19](#_ENREF_19)] | 5 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| Xie L, 2014 [[6](#_ENREF_6)] | 9 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| A study can be awarded a maximum of one ‘star’ (herein point) for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. Therefore, the maximum score for any one study is 9.  |

**References**

**1.** Kumagai N, Onishi K, Hoshino K, Nakamori S, Kitai T, Yazu T, et al. Improving drug adherence using fixed combinations caused beneficial treatment outcomes and decreased health-care costs in patients with hypertension. Clin Exp Hypertens2013; 35 (5):355-360.

**2.** Panjabi S, Lacey M, Bancroft T, Cao F. Treatment adherence, clinical outcomes, and economics of triple-drug therapy in hypertensive patients. J Am Soc Hypertens2013; 7 (1):46-60.

**3.** Bramlage P, Ketelhut R, Fronk EM, Wolf WP, Smolnik R, Zemmrich C, et al. Clinical impact of patient adherence to a fixed-dose combination of olmesartan, amlodipine and hydrochlorothiazide. Clin Drug Investig2014; 34 (6):403-411.

**4.** Degli Esposti L, Saragoni S, Buda S, Degli Esposti E. Drug adherence to olmesartan/amlodipine fixed combination in an Italian clinical practice setting. Clinicoecon Outcomes Res2014; 6:209-216.

**5.** Jadhav U, Hiremath J, Namjoshi DJ, Gujral VK, Tripathi KK, Siraj M, et al. Blood pressure control with a single-pill combination of indapamide sustained-release and amlodipine in patients with hypertension: the EFFICIENT study. PLoS One2014; 9 (4):e92955.

**6.** Xie L, Frech-Tamas F, Marrett E, Baser O. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. Curr Med Res Opin2014; 30 (12):2415-2422.

**7.** Czarnecka D, Koch EM, Gottwald-Hostalek U. Benefits of a fixed-dose combination of bisoprolol and amlodipine in the treatment of hypertension in daily practice: results of more than 4000 patients. Curr Med Res Opin2015; 31 (5):875-881.

**8.** Hsu CI, Hsiao FY, Wu FL, Shen LJ. Adherence and medication utilisation patterns of fixed-dose and free combination of angiotensin receptor blocker/thiazide diuretics among newly diagnosed hypertensive patients: a population-based cohort study. Int J Clin Pract2015; 69 (7):729-737.

**9.** Jung HW, Kim KI, Park CG, Kang DH, Ahn Y, Bae JH, et al. A multicenter, non-comparative study to evaluate the efficacy and safety of fixed-dose olmesartan/amlodipine in Korean patients with hypertension who are naive or non-responders to anti-hypertensive monotherapy (ACE-HY study). Clin Exp Hypertens2015; 37 (6):482-489.

**10.** Machnicki G, Ong SH, Chen W, Wei ZJ, Kahler KH. Comparison of amlodipine/valsartan/hydrochlorothiazide single pill combination and free combination: adherence, persistence, healthcare utilization and costs. Curr Med Res Opin2015; 31 (12):2287-2296.

**11.** Mancia G, Asmar R, Amodeo C, Mourad JJ, Taddei S, Gamba MA, et al. Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine. J Hypertens2015; 33 (2):401-411.

**12.** Manolis A, Grammatikou V, Kallistratos M, Zarifis J, Tsioufis K. Blood pressure reduction and control with fixed-dose combination perindopril/amlodipine: A Pan-Hellenic prospective observational study. J Renin Angiotensin Aldosterone Syst2015; 16 (4):930-935.

**13.** Rosenkranz AR, Ratzinger M. Efficacy, safety, and tolerability of antihypertensive therapy with aliskiren/amlodipine in clinical practice in Austria. The RALLY (Rasilamlo long lasting efficacy) study. Wien Klin Wochenschr2015; 127 (5-6):203-209.

**14.** Setiawati A, Kalim H, Abdillah A. Clinical effectiveness, safety and tolerability of amlodipine/valsartan in hypertensive patients: the Indonesian subset of the EXCITE study. Acta Med Indones2015; 47 (3):223-233.

**15.** Tung YC, Lin YS, Wu LS, Chang CJ, Chu PH. Clinical outcomes and healthcare costs in hypertensive patients treated with a fixed-dose combination of amlodipine/valsartan. J Clin Hypertens (Greenwich)2015; 17 (1):51-58.

**16.** Assaad-Khalil SH, Nashaat N. Real-life effectiveness and safety of amlodipine/valsartan single-pill combination in patients with hypertension in Egypt: results from the EXCITE study. Drugs Real World Outcomes2016; 3 (3):307-315.

**17.** Levi M, Pasqua A, Cricelli I, Cricelli C, Piccinni C, Parretti D, et al. Patient adherence to olmesartan/amlodipine combinations: fixed versus extemporaneous combinations. J Manag Care Spec Pharm2016; 22 (3):255-262.

**18.** Simonyi G, Ferenci T, Alfoldi S, Farsang C. Ramipril + amlodipine and ramipril + hydrochlorothiazide fixed-dose combinations in relation to patient adherence. J Int Med Res2016; 44 (5):1087-1091.

**19.** Vlachopoulos C, Grammatikou V, Kallistratos M, Karagiannis A. Effectiveness of perindopril/amlodipine fixed dose combination in everyday clinical practice: results from the EMERALD study. Curr Med Res Opin2016; 32 (9):1605-1610.

**20.** Lauffenburger JC, Landon JE, Fischer MA. Effect of combination therapy on adherence among US patients initiating therapy for hypertension: a cohort study. J Gen Intern Med2017; 32 (6):619-625.

**21.** Liakos CI, Papadopoulos DP, Kotsis VT. Adherence to treatment, safety, tolerance, and effectiveness of perindopril/amlodipine fixed-dose combination in Greek patients with hypertension and stable coronary artery disease: A pan-Hellenic prospective observational study of daily clinical practice. Am J Cardiovasc Drugs2017; 17 (5):391-398.

**22.** Mourad JJ, Amodeo C, de Champvallins M, Brzozowska-Villatte R, Asmar R, study coordinators, et al. Blood pressure-lowering efficacy and safety of perindopril/indapamide/amlodipine single-pill combination in patients with uncontrolled essential hypertension: a multicenter, randomized, double-blind, controlled trial. J Hypertens2017; 35 (7):1481-1495.

**23.** Nedogoda SV, Stojanov VJ. Single-pill combination of perindopril/indapamide/amlodipine in patients with uncontrolled hypertension: a randomized controlled trial. Cardiol Ther2017; 6 (1):91-104.

**24.** Simons LA, Chung E, Ortiz M. Long-term persistence with single-pill, fixed-dose combination therapy versus two pills of amlodipine and perindopril for hypertension: Australian experience. Curr Med Res Opin2017; 33 (10):1783-1787.

**25.** Bramlage P, Schmidt S, Sims H. Fixed-dose vs free-dose combinations for the management of hypertension-An analysis of 81 958 patients. J Clin Hypertens (Greenwich)2018; 20 (4):705-715.

**26.** Degli Esposti L, Perrone V, Veronesi C, Gambera M, Nati G, Perone F, et al. Modifications in drug adherence after switch to fixed-dose combination of perindopril/amlodipine in clinical practice. Results of a large-scale Italian experience. The amlodipine-perindopril in real settings (AMPERES) study. Curr Med Res Opin2018; 34 (9):1571-1577.

**27.** Fleig SV, Weger B, Haller H, Limbourg FP. Effectiveness of a fixed-dose, single-pill combination of perindopril and amlodipine in patients with hypertension: a non-interventional study. Adv Ther2018; 35 (3):353-366.

**28.** Verma AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: A population-based retrospective cohort study. PLoS Med2018; 15 (6):e1002584.

**29.** Webster R, Salam A, de Silva HA, Selak V, Stepien S, Rajapakse S, et al. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: A randomized clinical trial. JAMA2018; 320 (6):566-579.

**30.** National Institute for Health and Care Excellence (NICE). Guide to the single technology appraisal process. 2009.

**31.** Wells G, Shea B, O’Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle-Ottawa scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses.