

TABLES

Table 33: Antihypertensive prescriptions and expenditure for British Columbia

	Claims/Prescriptions					Expenditure				
	2001/2	2002/3	2003/4	2004/5	2005/6	2001/2	2002/3	2003/4	2004/5	2005/6
Thiazides	424,786	340,230	494,506	594,374	656,862	\$2,182,794	\$2,733,412	\$4,543,765	\$5,422,976	\$5,865,398
Beta blockers	493,616	487,009	501,423	583,682	644,731	\$12,114,560	\$11,214,171	\$11,475,621	\$12,792,200	\$12,972,628
CCBs	468,718	495,482	464,817	541,120	612,558	\$34,548,740	\$34,705,347	\$29,529,332	\$33,006,017	\$35,118,731
ACE inhibitors	628,388	688,694	653,851	764,961	859,708	\$39,754,829	\$41,985,273	\$35,973,120	\$40,046,082	\$42,216,122
ARBs	53,392	71,360	77,515	101,219	124,499	\$4,638,297	\$5,896,994	\$5,554,537	\$6,954,013	\$8,119,119

Data obtained from British Columbia Ministry of Health (Brett Wilmer, Pharmaceutical Services, PharmaNet and Evaluation: personal communication, 2007 Mar 19)

Table 34: Antihypertensive prescriptions and expenditure for New Brunswick

	Claims/Prescriptions					Expenditure				
	2001/2	2002/3	2003/4	2004/5	2005/6	2001/2	2002/3	2003/4	2004/5	2005/6
Thiazides	70898	75053	83692	88845	92433	\$359,003	\$410,812	\$454,484	\$480,453	\$497,702
Beta blockers	97268	101813	108853	114522	119115	\$2,275,756	\$2,369,649	\$2,554,936	\$2,600,809	\$2,736,997
CCBs	103165	105537	107544	108721	111317	\$6,553,644	\$6,980,028	\$7,500,466	\$8,031,792	\$8,595,317
ACE inhibitors	128988	134372	138563	142443	148589	\$7,395,286	\$7,984,214	\$8,541,349	\$8,971,265	\$9,368,967
ARBs	11941	16236	19503	22639	27160	\$724,566	\$1,028,023	\$1,307,735	\$1,622,307	\$2,025,222

Data obtained from New Brunswick Ministry of Health (Brenda Currie, New Brunswick Prescription Drug Program: personal communication, 2007 Mar 15)

Table 35: Antihypertensive prescriptions and expenditure for PEI

	Claims/Prescriptions			Expenditure		
	2003/4	2004/5	2005/6	2003/4	2004/5	2005/6
Thiazides	5157	5614	6239	30463	28376	30569
Beta blockers	17962	19438	20646	400234	414880	440124
CCBs	19586	20975	21699	1763120	1962926	2102750
ACE inhibitors	21943	23460	20929	1599140	1688168	1766958
ARBs	6274	7198	8332	462778	560318	662522

Data obtained from Prince Edward Island Ministry of Health (Patrick Crawford, Prince Edward Island Drug Programs, Department of Social Services and Seniors: personal communication, 2007 Mar 5)

Table 36: Antihypertensive prescriptions and expenditure for Nova Scotia

	Claims/Prescriptions					Expenditure				
	2001/2	2002/3	2003/4	2004/5	2005/6	2001/2	2002/3	2003/4	2004/5	2005/6
Thiazides	88,349	94,819	105,931	110,343	113,435	814,104	948,489	1,037,398	1,106,273	1,150,958
Beta blockers	178,614	191,061	202,489	207,867	211,884	4,027,833	4,358,541	4,562,862	4,719,272	4,951,383
CCBs	152,521	159,421	162,603	163,785	165,138	9,017,858	9,613,267	10,425,237	11,201,819	11,944,096
ACE inhibitors	191,742	204,071	208,997	211,931	213,491	9,652,914	10,382,272	11,033,984	11,474,074	11,793,666
ARBs	44,279	59,184	70,665	79,375	87,516	2,400,952	3,247,916	4,028,424	4,768,758	5,551,939

Data obtained from Nova Scotia Department of Health (Judy McPhee, Nova Scotia Drug Programs: personal communication, 2007 Apr 20)

Table 37: Antihypertensive prescriptions and expenditure for Manitoba

	Claims/Prescriptions					Expenditure				
	2001/2	2002/3	2003/4	2004/5	2005/6	2001/2	2002/3	2003/4	2004/5	2005/6
Thiazides	56,627	66,384	79,084	83,088	90,859	483,865.38	658,032	848,518	917,460	1,006,915
Beta blocker	105,322	124,249	142,544	153,639	172,507	2,501,095.46	2,965,580	3,464,726	3,519,979	3,768,503
CCB	136,433	151,417	163,300	168,984	184,438	8,142,424.08	9,133,418	10,271,256	10,832,314	11,544,365
ACE inhibitors	173,167	190,240	201,255	203,591	219,379	8,911,302.18	9,822,364	10,516,330	10,169,759	10,397,632
ARB	39,066	49,532	57,012	62,505	68,532	2,236,091.98	2,831,587	3,304,797	3,647,170	4,035,941

Data obtained from the Canadian Institute for Health Information (Ruzica Subotic-Howell, CIHI: personal communication, 2007 Apr 4)

Table 38: Antihypertensive prescriptions and expenditure for Saskatchewan

	Claims/Prescriptions				Expenditure			
	2001/2	2002/3	2003/4	2004/5	2001/2	2002/3	2003/4	2004/5
Thiazides	80,312	92,998	86,841	87,536	453,050	572,108	613,104	629,967
Beta blockers	131,574	150,450	169,881	197,608	1,362,292	1,853,884	2,311,842	2,375,896
CCBs	178,981	193,374	204,926	223,760	6,144,969	6,789,096	7,473,312	8,462,641
ACE inhibitors	220,656	240,876	253,423	277,429	6,386,471	7,042,855	7,606,005	8,145,905
ARBs	57,131	72,749	83,910	99,564	1,853,638	2,359,057	2,762,146	3,332,687

Data were in 2004-2005 and obtained from the Canadian Institute for Health Information (Ruzica Subotic-Howell, CIHI: personal communication, 2007 Apr 4))

Table 39: Proportion of antihypertensive therapeutic class prescribed for hypertension

Therapeutic Class	Proportion of Prescriptions for Hypertension
Thiazides	0.828
Beta blockers	0.42
CCBs	0.709
ACE inhibitors	0.674
ARBs	0.816

Table 40: Budget impact analysis

Province	Year	Projected budget impact of switch to thiazide diuretics with corresponding percentage reduction in non-thiazide therapeutic classes			
		0%	5%	10%	25%
BC	2006/2007	\$75,354,053	\$72,511,907	\$69,669,760	\$61,143,321
	2007/2008	\$80,423,776	\$77,391,942	\$74,360,107	\$65,264,603
	2008/2009	\$85,493,500	\$82,271,977	\$79,050,454	\$69,385,885
PEI	2006/2007	\$3,557,393	\$3,392,357	\$3,227,322	\$2,732,216
	2007/2008	\$3,682,127	\$3,511,408	\$3,340,689	\$2,828,533
	2008/2009	\$3,806,861	\$3,630,459	\$3,454,057	\$2,924,851
New Brunswick	2006/2007	\$16,251,204	\$15,530,832	\$14,810,460	\$12,649,345
	2007/2008	\$16,879,149	\$16,131,311	\$15,383,474	\$13,139,962
	2008/2009	\$17,507,094	\$16,731,791	\$15,956,488	\$13,630,580
Manitoba	2006/2007	\$27,526,223	\$26,500,830	\$25,475,437	\$22,399,257
	2007/2008	\$34,149,663	\$32,876,806	\$31,603,948	\$27,785,375
	2008/2009	\$40,773,103	\$39,252,782	\$37,732,460	\$33,171,494
Saskatchewan	2006/2007	\$28,798,795	\$27,742,759	\$26,686,723	\$23,518,616
	2007/2008	\$35,333,536	\$34,037,940	\$32,742,344	\$28,855,557
	2008/2009	\$41,868,276	\$40,333,120	\$38,797,965	\$34,192,498
Nova Scotia	2006/2007	\$25,038,165	\$24,059,564	\$23,080,964	\$20,145,162
	2007/2008	\$26,096,062	\$25,076,441	\$24,056,820	\$20,997,957
	2008/2009	\$27,153,959	\$26,093,318	\$25,032,676	\$21,850,752

FIGURES

Figure 1: Selection of trials related to thiazide diuretics versus placebo or no treatment and other antihypertensive drug classes

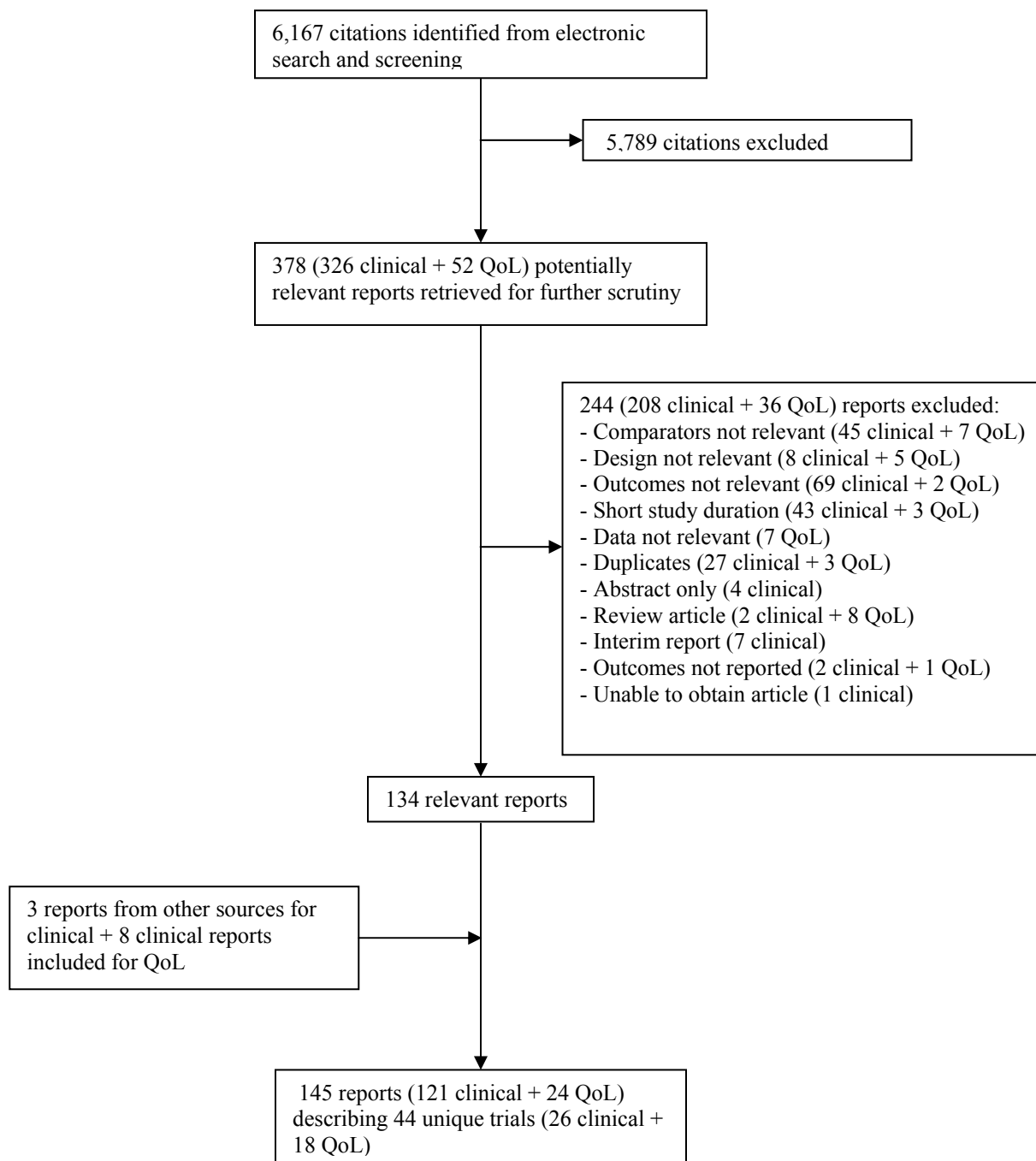


Figure 2: Selection of trials related to BP target

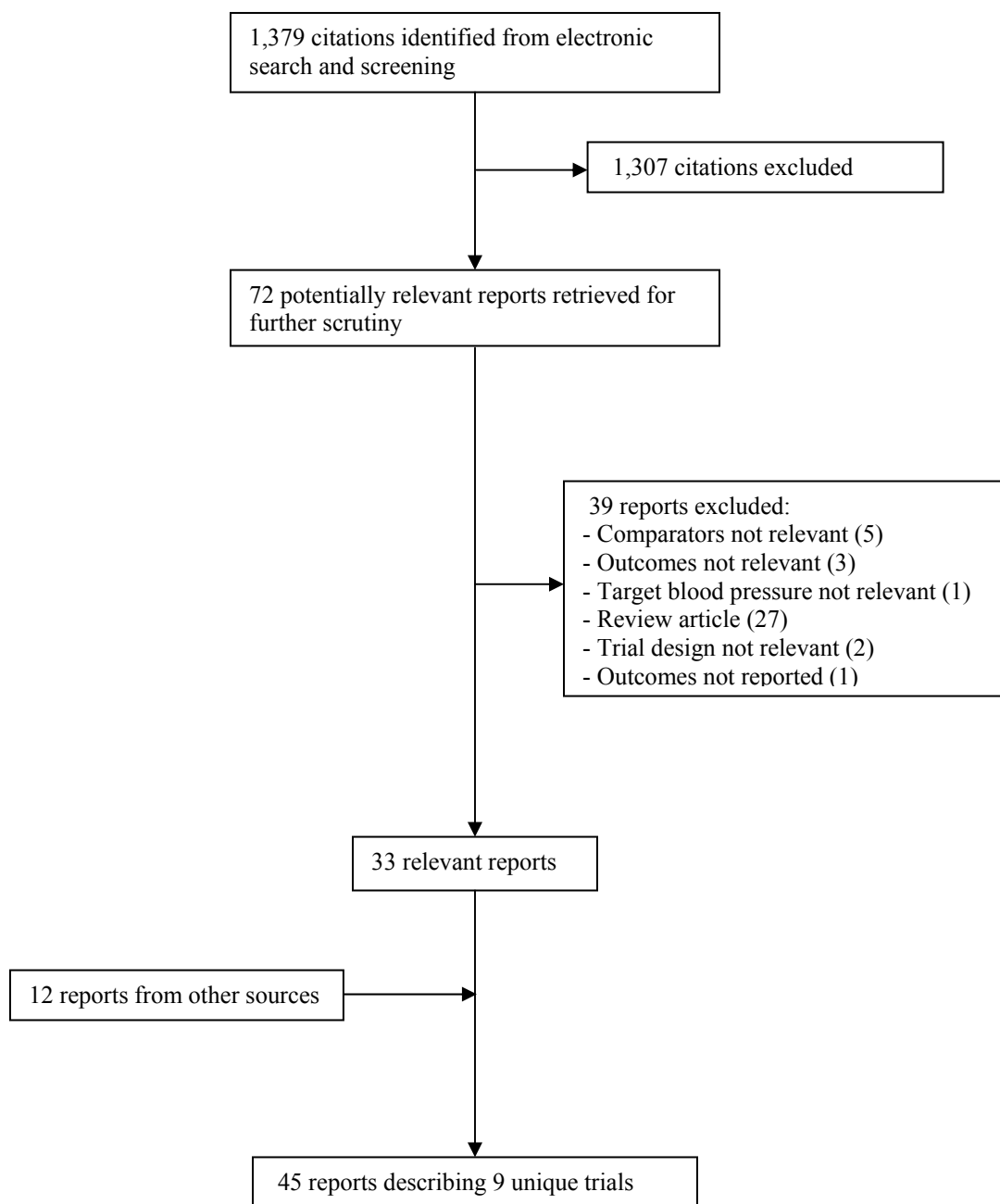


Figure 3: All cardiovascular events (thiazide diuretics versus placebo or no treatment)

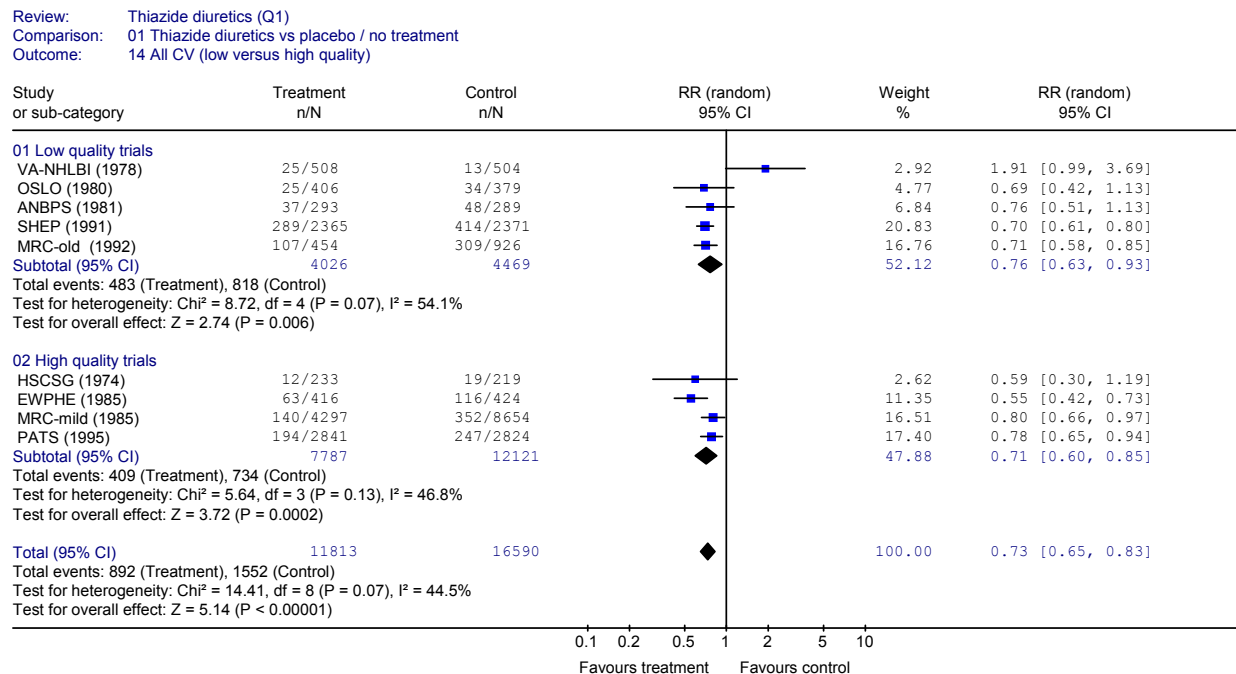
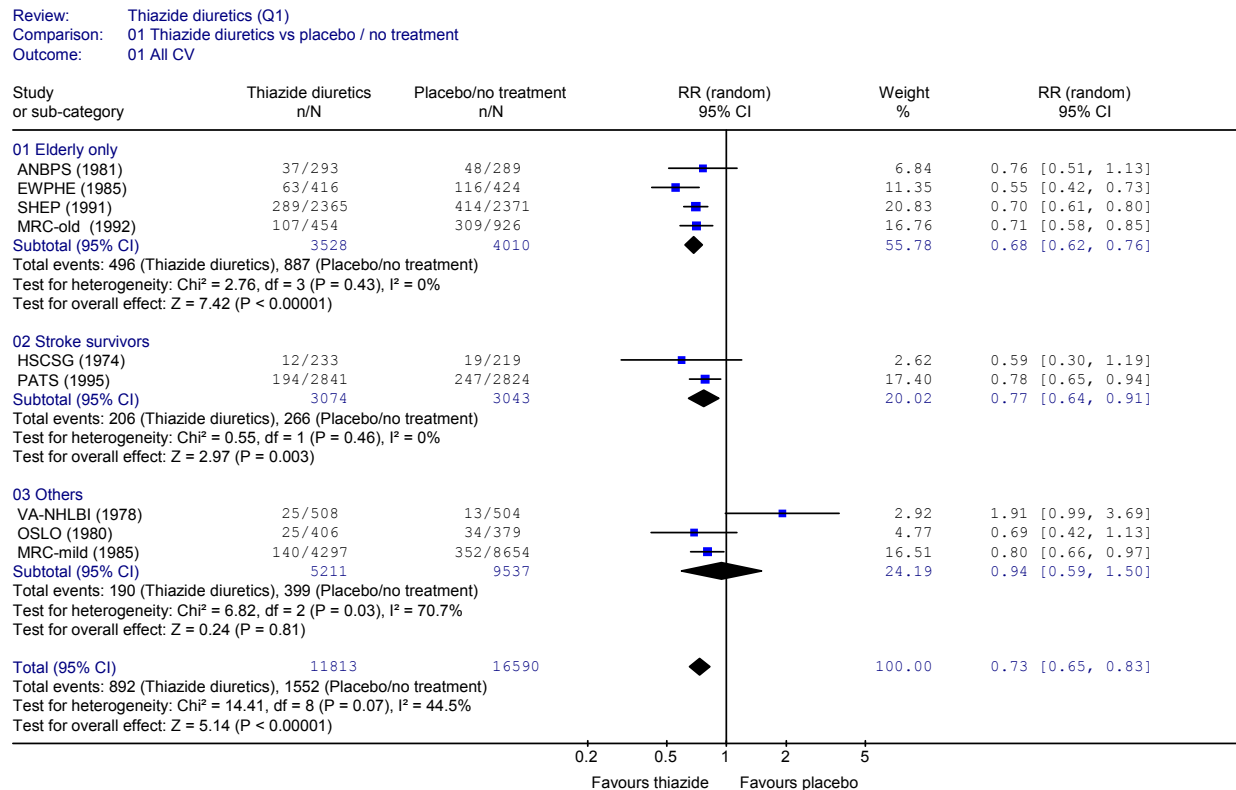


Figure 4: Coronary heart disease events (thiazide diuretics versus placebo or no treatment)

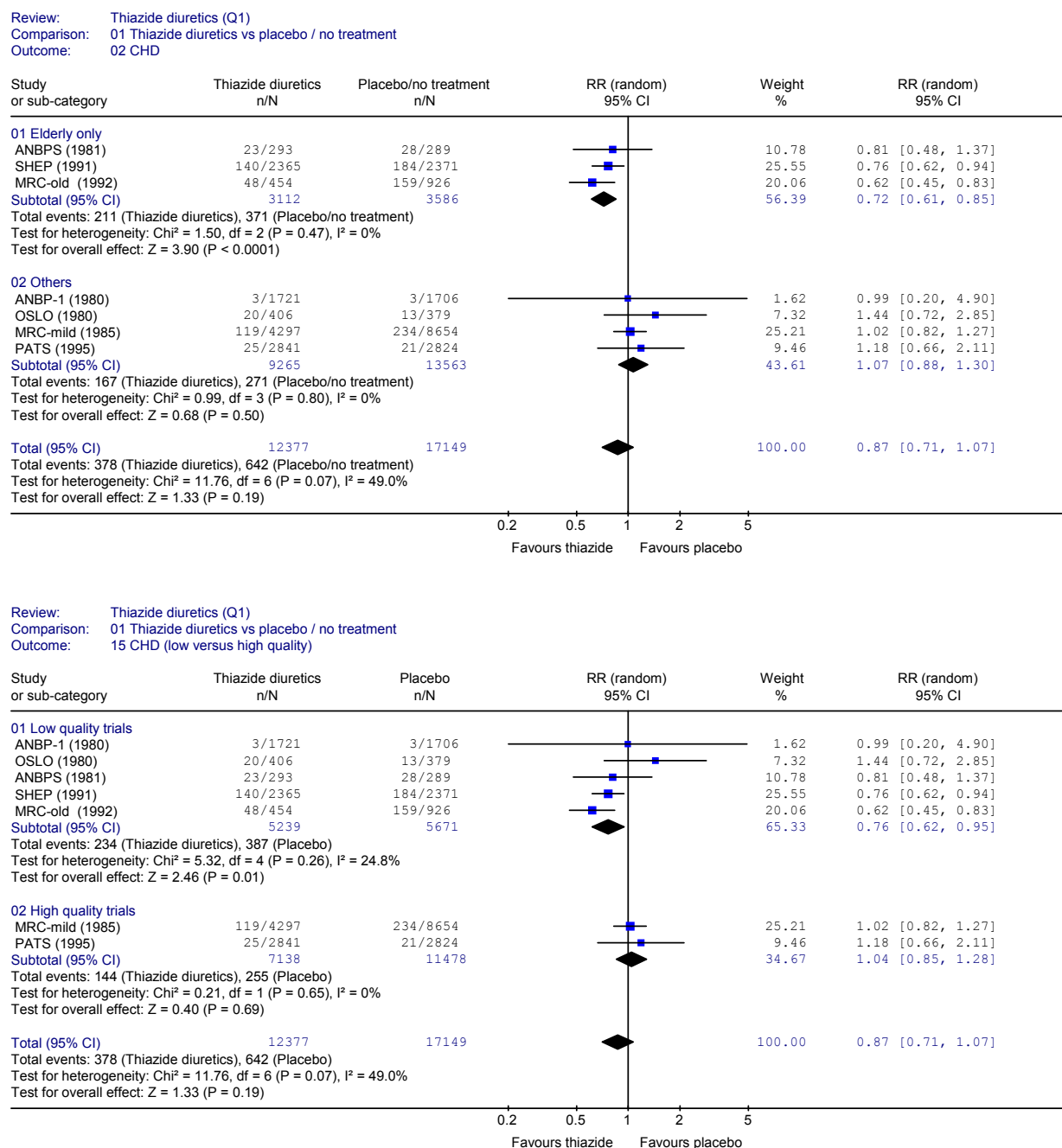
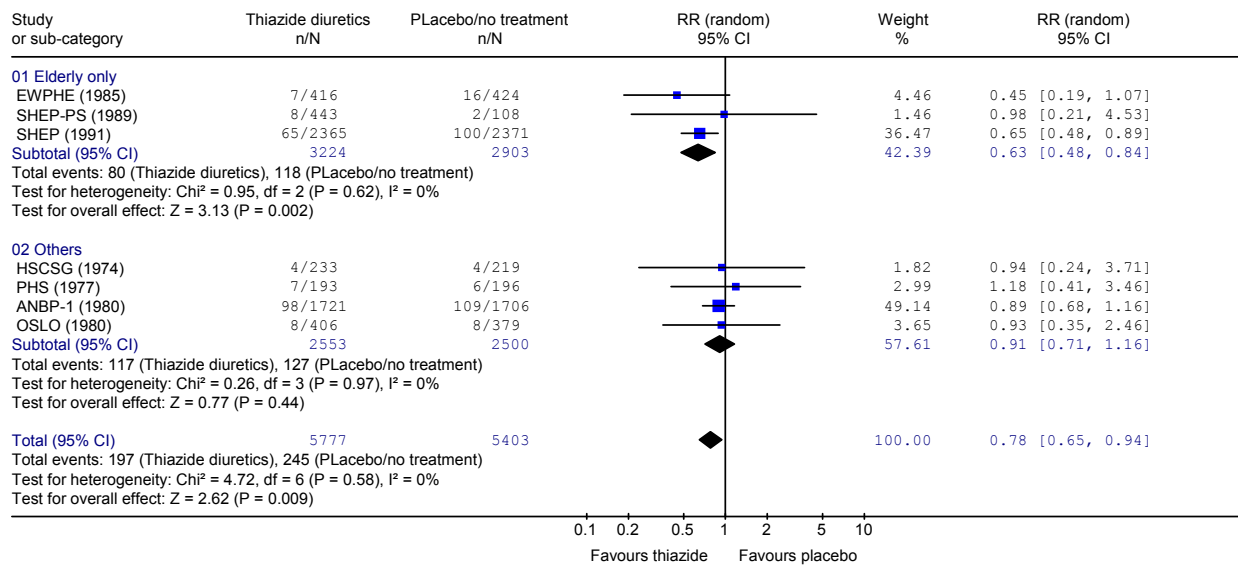


Figure 5: Myocardial infarction events (thiazide diuretics versus placebo or no treatment)

Review: Thiazide diuretics (Q1)

Comparison: 01 Thiazide diuretics vs placebo / no treatment

Outcome: 03 MI



Review: Thiazide diuretics (Q1)

Comparison: 01 Thiazide diuretics vs placebo / no treatment

Outcome: 16 MI (low versus high quality)

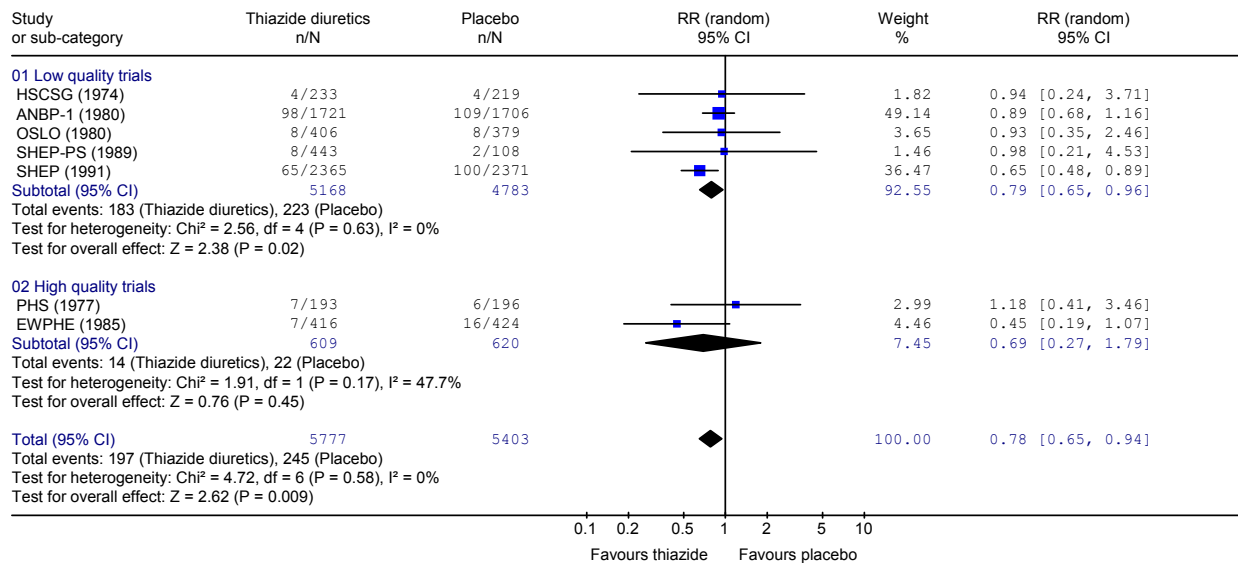


Figure 6: Heart failure events (thiazide diuretics versus placebo or no treatment)

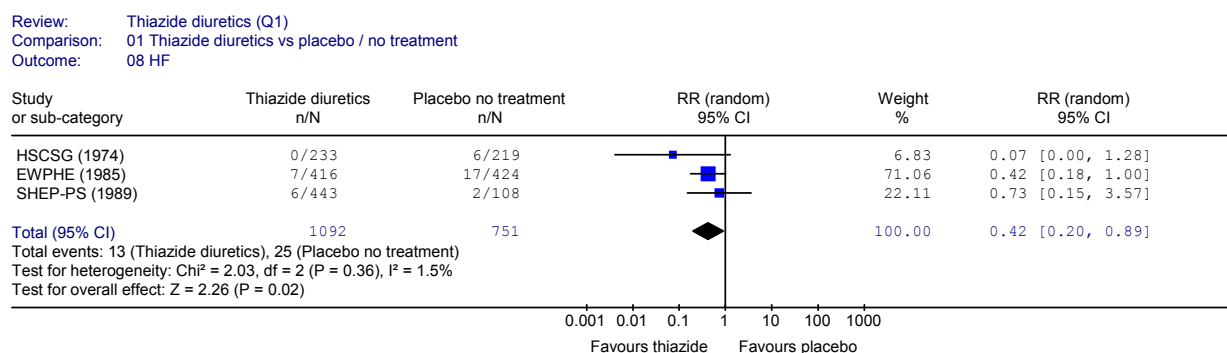
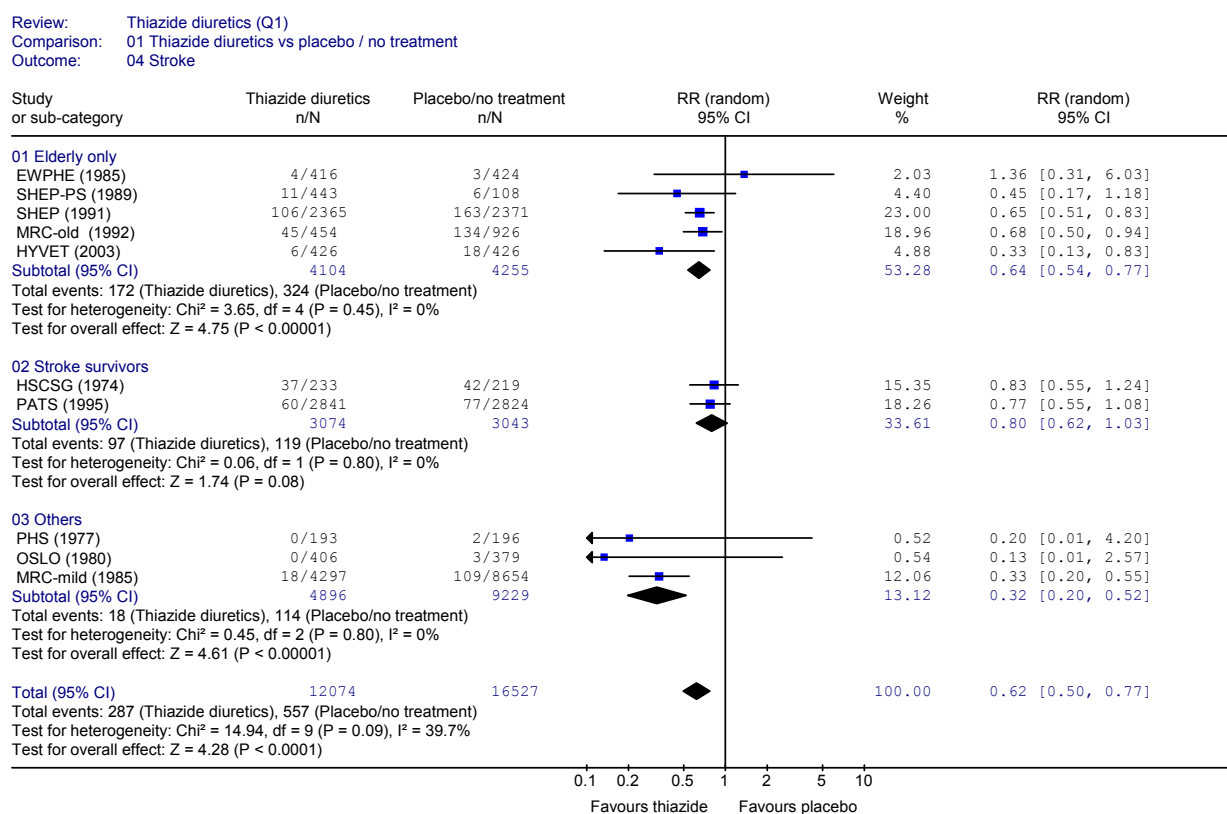


Figure 7: Stroke events (thiazide diuretics versus placebo or no treatment)



Review: Thiazide diuretics (Q1)
 Comparison: 01 Thiazide diuretics vs placebo / no treatment
 Outcome: 17 Stroke (low versus high quality)

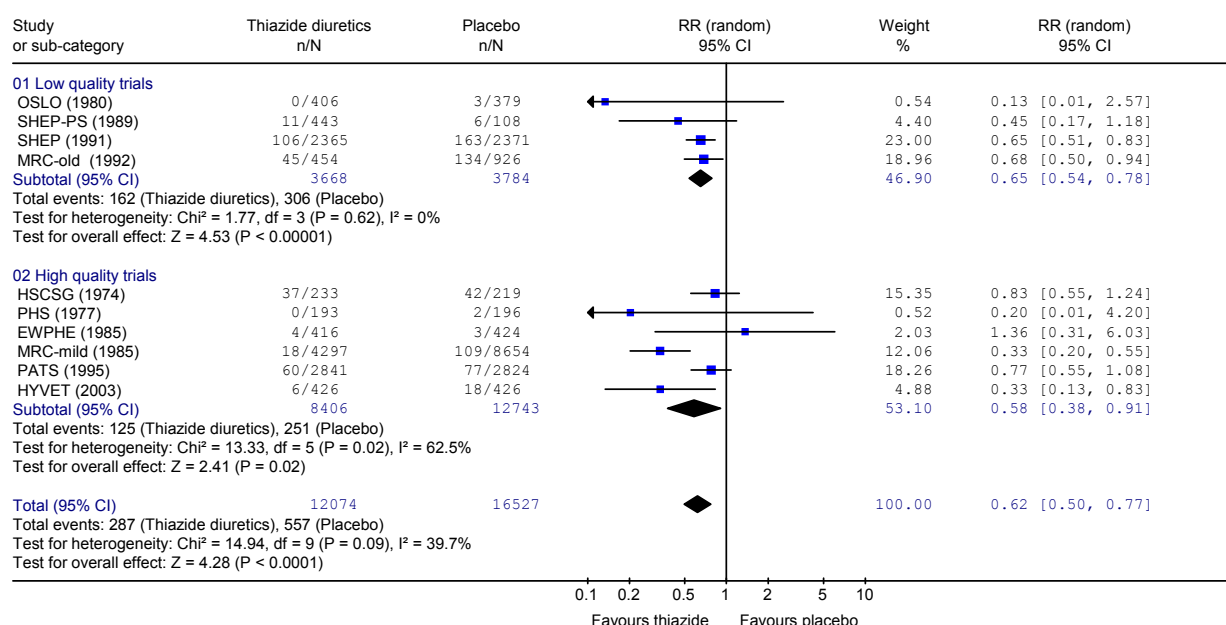


Figure 8: Cerebrovascular events (thiazide diuretics versus placebo or no treatment)

Review: Thiazide diuretics (Q1)
 Comparison: 01 Thiazide diuretics vs placebo / no treatment
 Outcome: 05 CRV

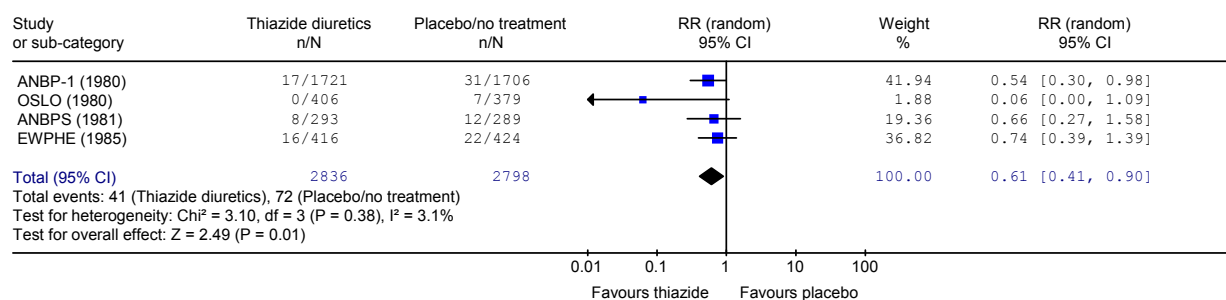


Figure 9: Renal failure events (thiazide diuretics versus placebo or no treatment)

Review: Thiazide diuretics (Q1)
 Comparison: 01 Thiazide diuretics vs placebo / no treatment
 Outcome: 09 RF

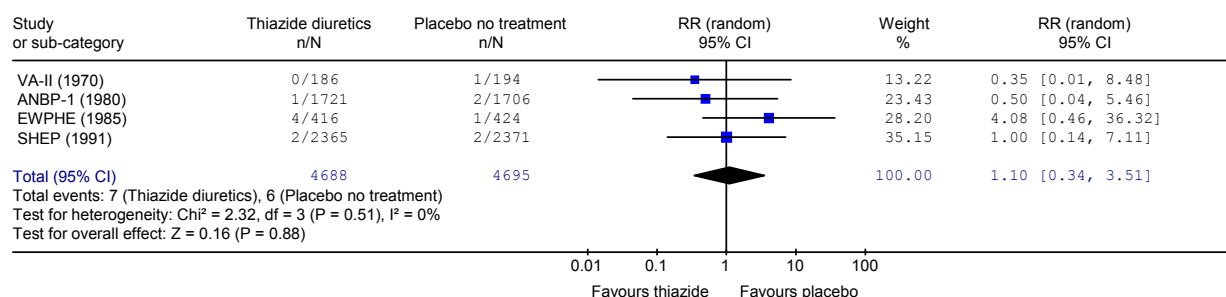


Figure 10: Cardiovascular deaths (thiazide diuretics versus placebo or no treatment)

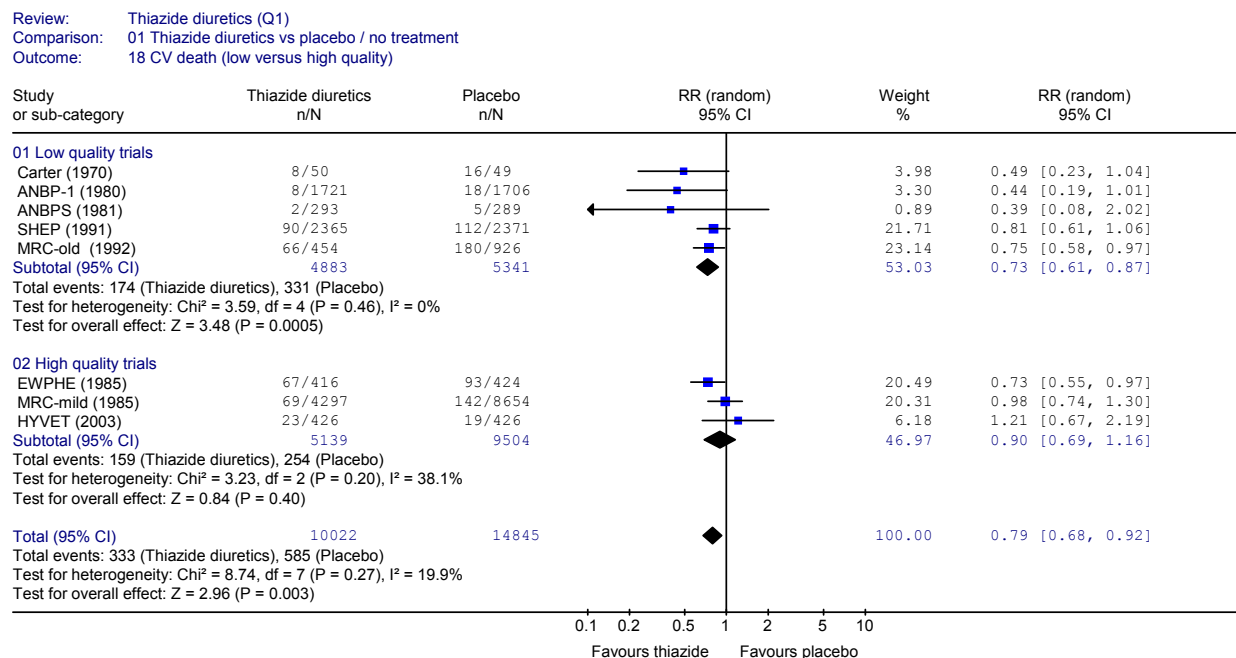
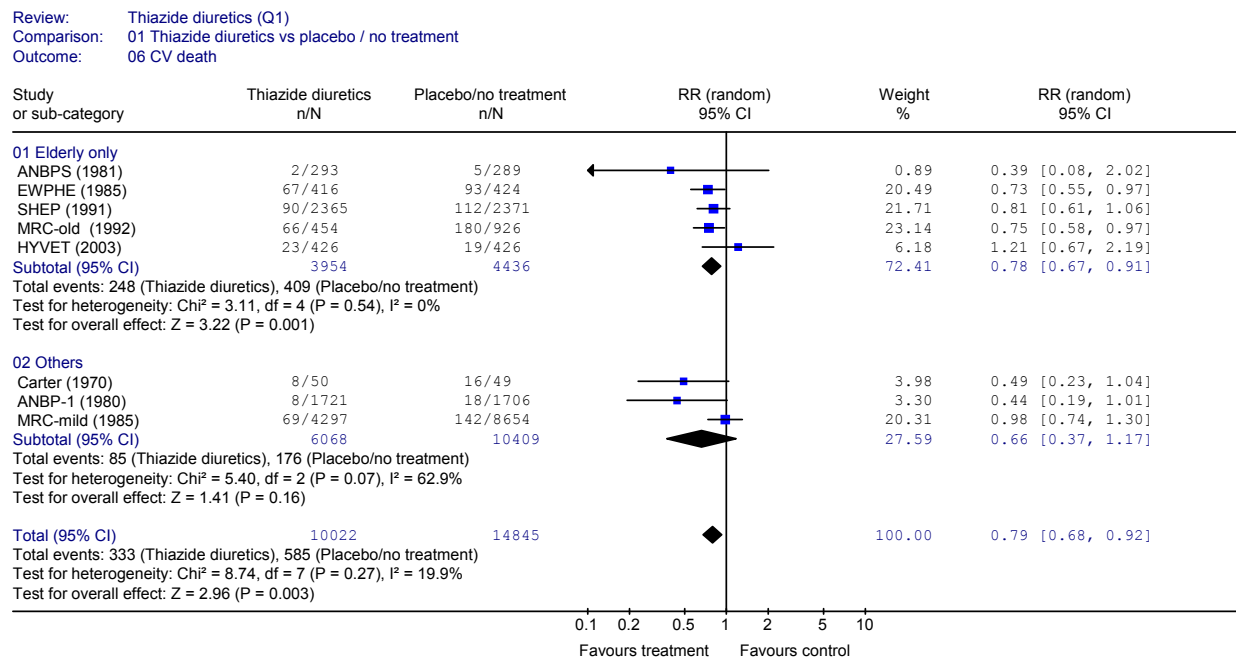


Figure 11: All deaths (thiazide diuretics versus placebo or no treatment)

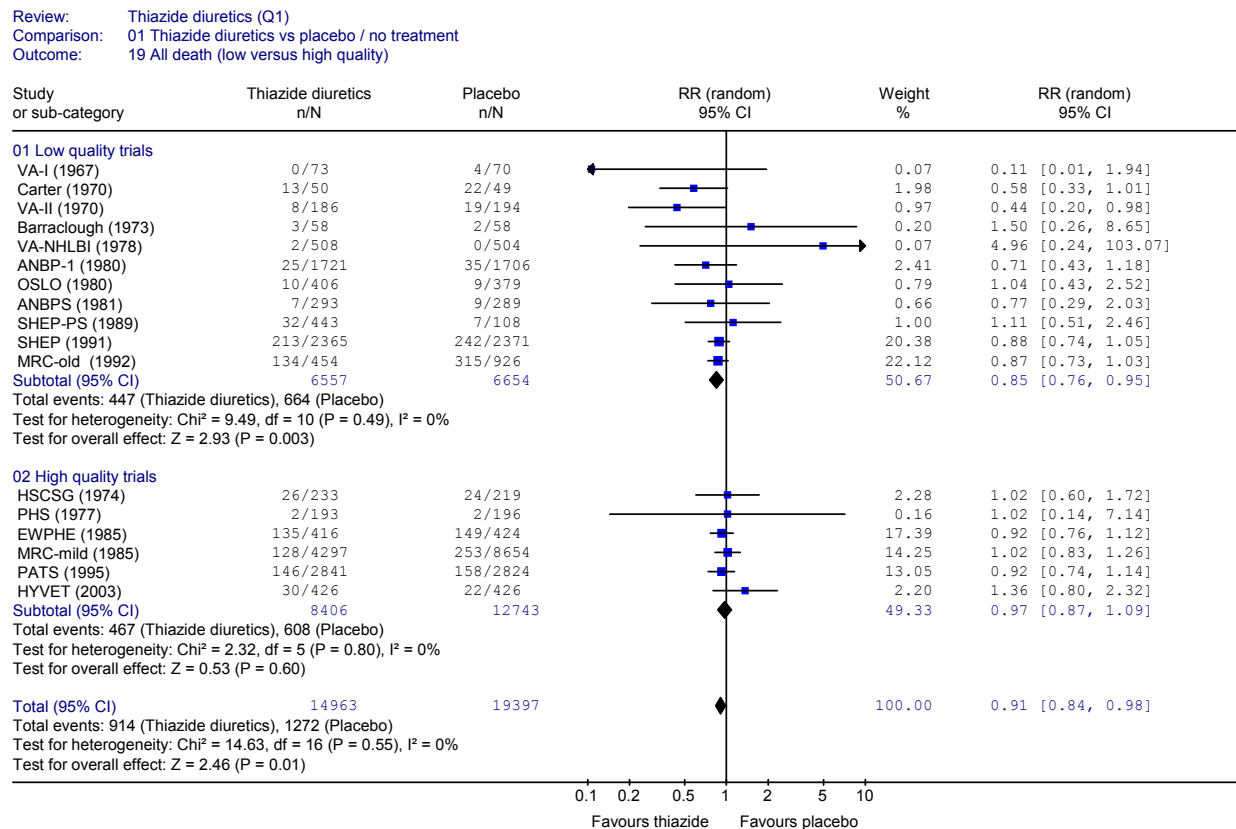


Figure 12: Withdrawals due to adverse events (thiazide diuretics versus placebo or no treatment)

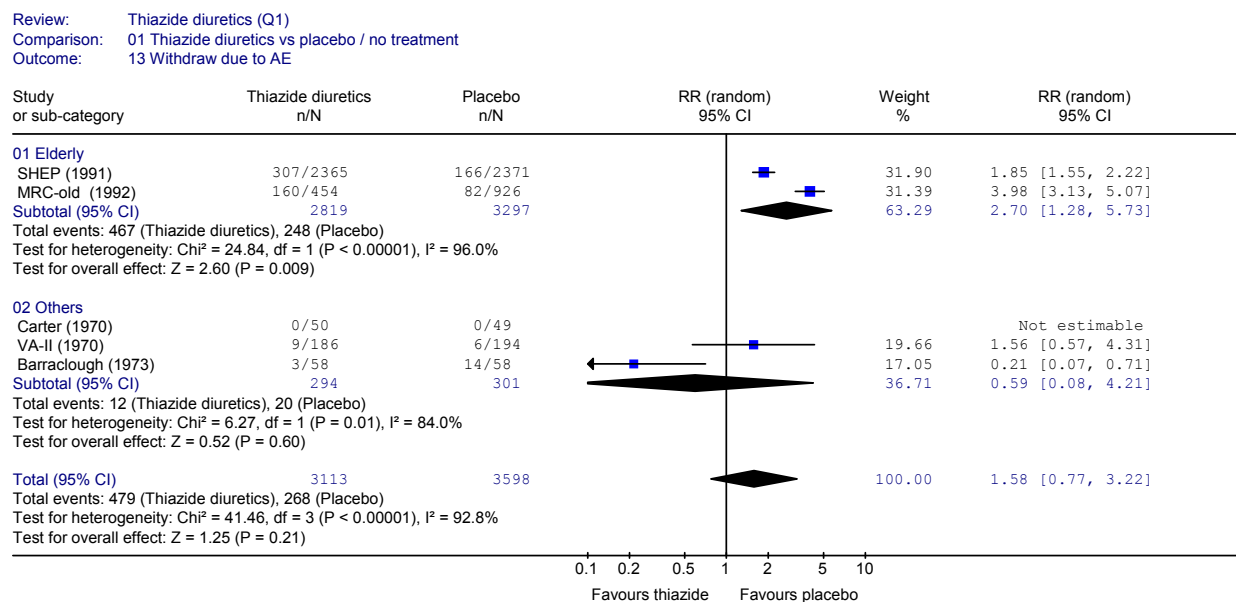


Figure 13: SBP (thiazide diuretics versus placebo or no treatment)

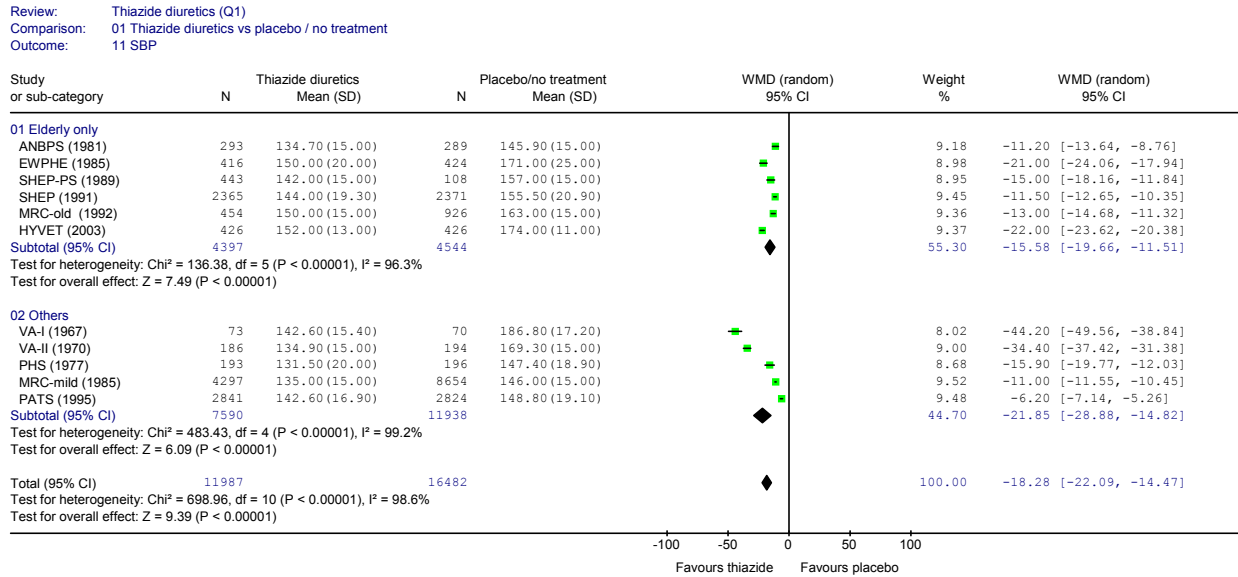


Figure 14: DBP (thiazide diuretics versus placebo or no treatment)

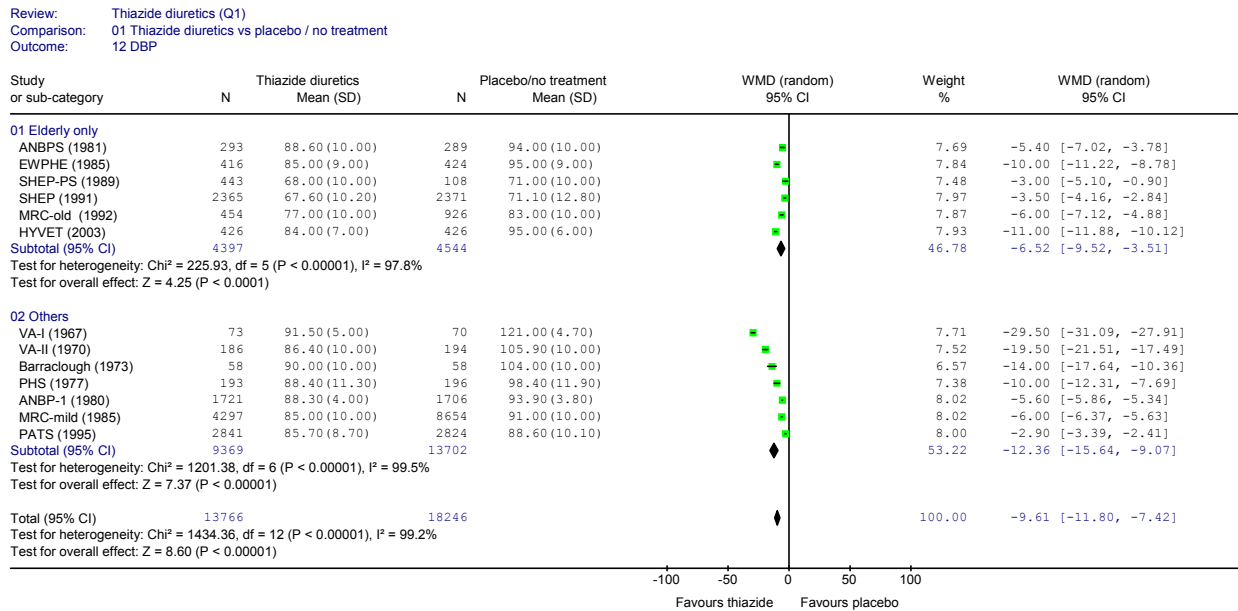


Figure 15: All cardiovascular events (thiazide diuretics versus ACE inhibitors)

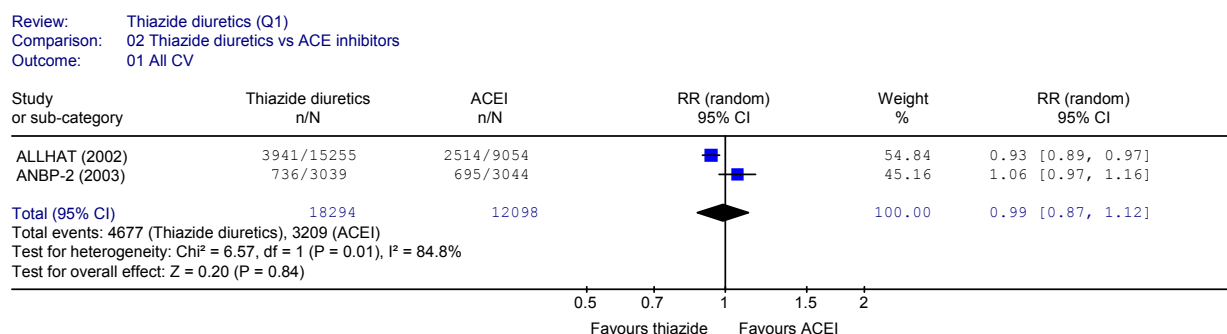


Figure 16: Coronary heart disease events (thiazide diuretics versus ACE inhibitors)

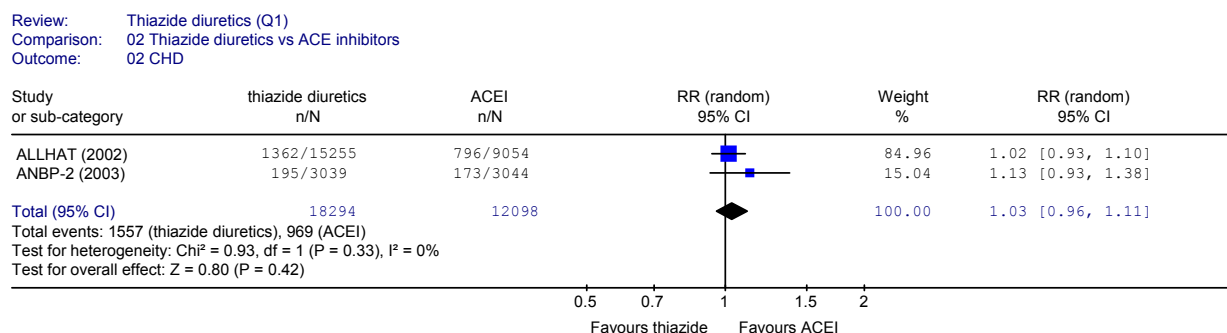


Figure 17: Heart failure events (thiazide diuretics versus ACE inhibitors)

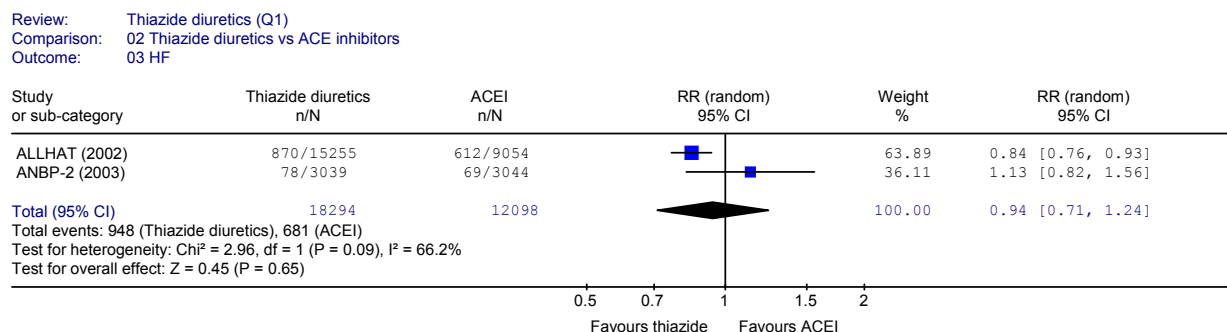


Figure 18: Stroke events (thiazide diuretics versus ACE inhibitors)

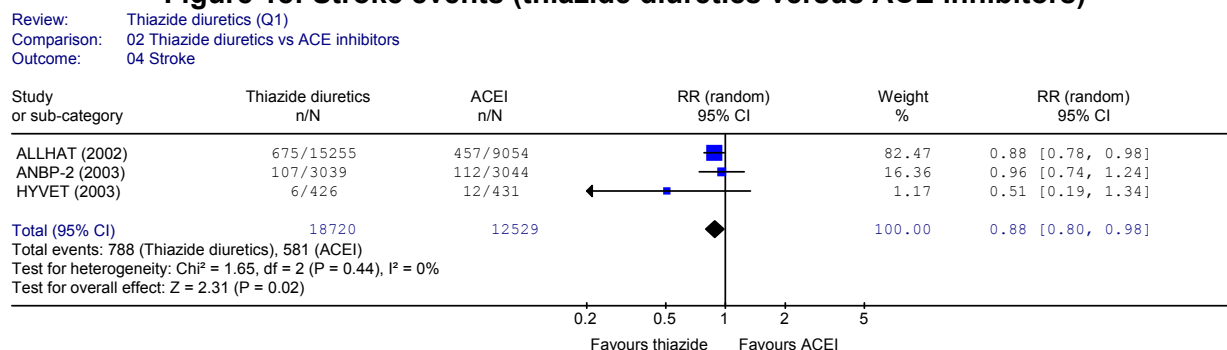


Figure 19: All deaths (thiazide diuretics versus ACE inhibitors)

Review: Thiazide diuretics (Q1)
Comparison: 02 Thiazide diuretics vs ACE inhibitors
Outcome: 05 All death

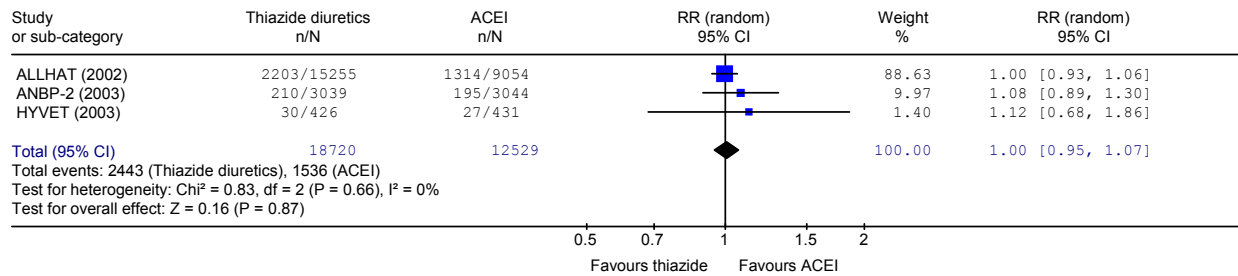


Figure 20: Withdrawals due to adverse events (thiazide diuretics versus ACE inhibitors)

Review: Thiazide diuretics (Q1)
Comparison: 02 Thiazide diuretics vs ACE inhibitors
Outcome: 06 Withdraw

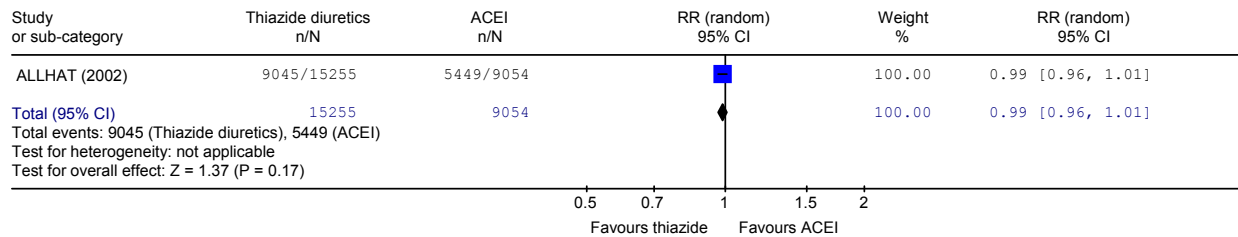


Figure 21: SBP (thiazide diuretics versus ACE inhibitors)

Review: Thiazide diuretics (Q1)
Comparison: 02 Thiazide diuretics vs ACE inhibitors
Outcome: 07 SBP

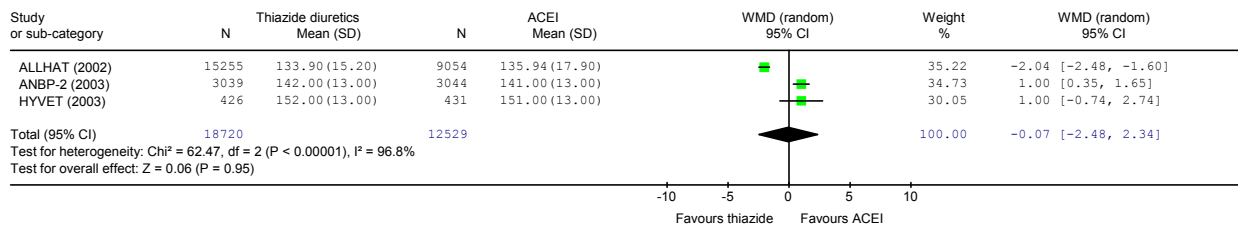


Figure 22: DBP (thiazide diuretics versus ACE inhibitors)

Review: Thiazide diuretics (Q1)
Comparison: 02 Thiazide diuretics vs ACE inhibitors
Outcome: 08 DBP

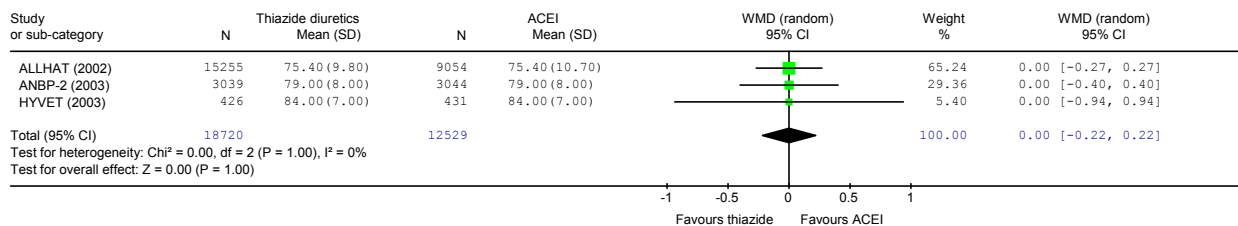


Figure 23: All cardiovascular events (thiazide diuretics versus BB)

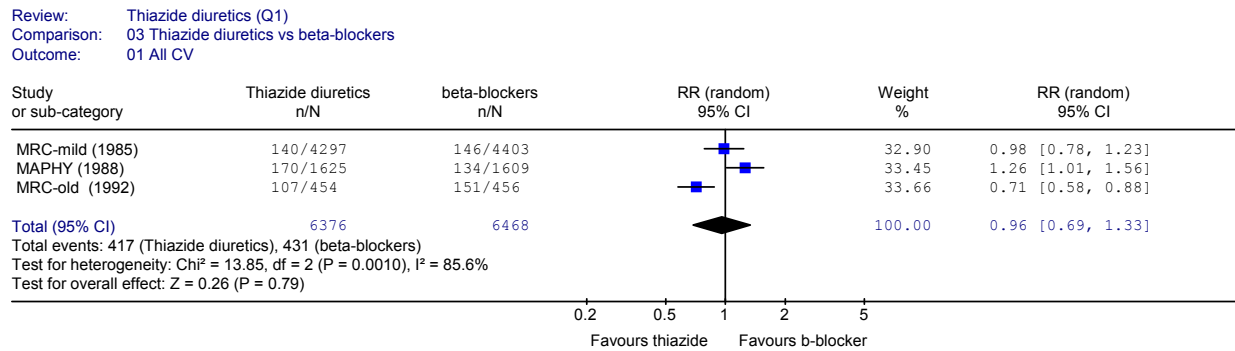


Figure 24: Coronary heart disease events (thiazide diuretics versus BB)

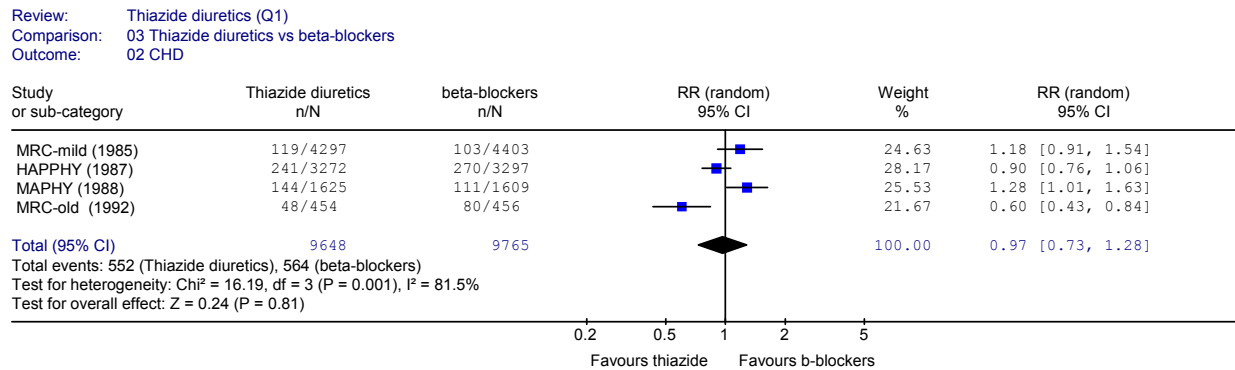


Figure 25: Stroke events (thiazide diuretics versus BB)

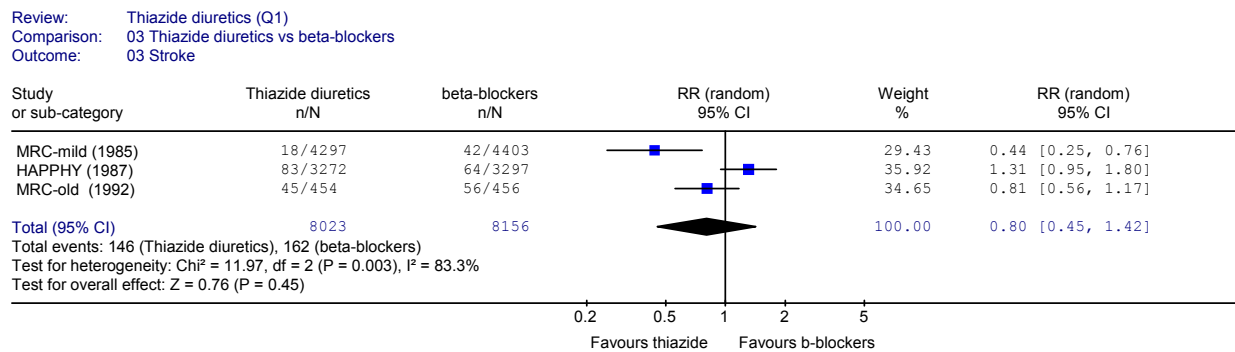


Figure 26: Cardiovascular deaths (thiazide diuretics versus BB)

Review: Thiazide diuretics (Q1)
Comparison: 03 Thiazide diuretics vs beta-blockers
Outcome: 04 CV death

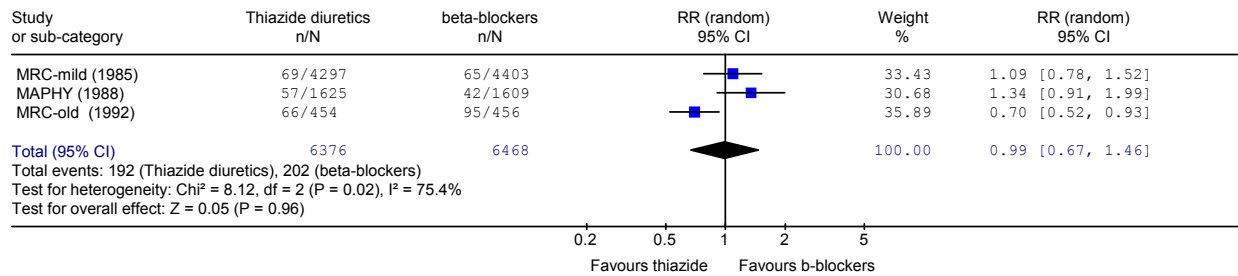


Figure 27: All deaths (thiazide diuretics versus BB)

Review: Thiazide diuretics (Q1)
Comparison: 03 Thiazide diuretics vs beta-blockers
Outcome: 05 All death

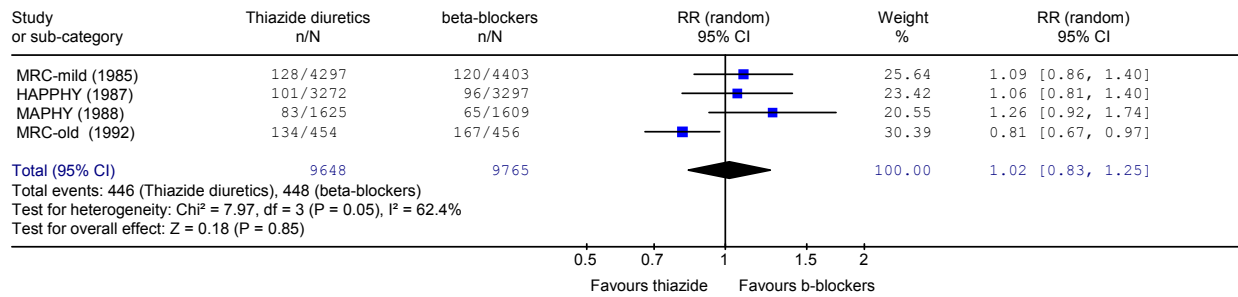


Figure 28: Withdrawals due to adverse events (thiazide diuretics versus BB)

Review: Thiazide diuretics (Q1)
Comparison: 03 Thiazide diuretics vs beta-blockers
Outcome: 06 Withdraw due to AE

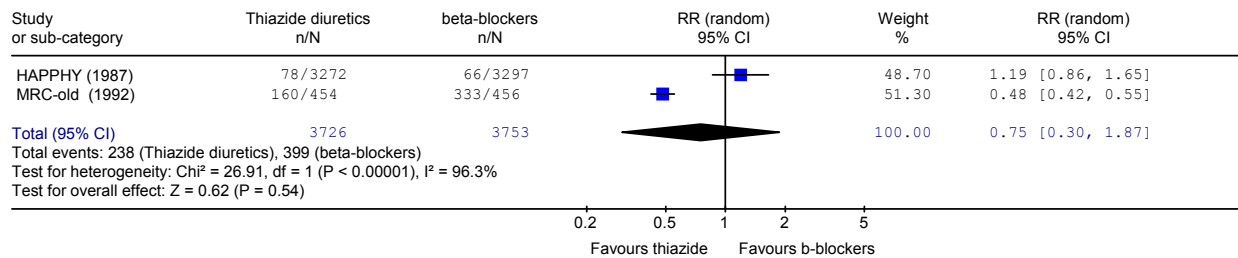


Figure 29: SBP (thiazide diuretics versus BB)

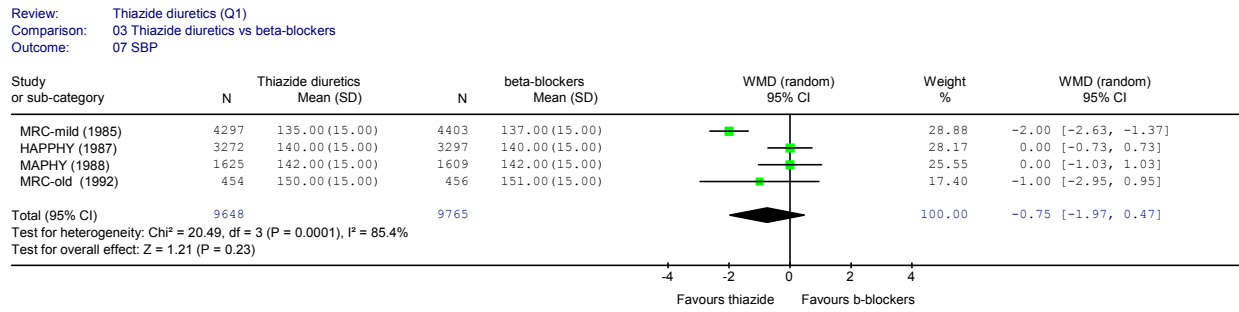


Figure 30: DBP (thiazide diuretics versus BB)

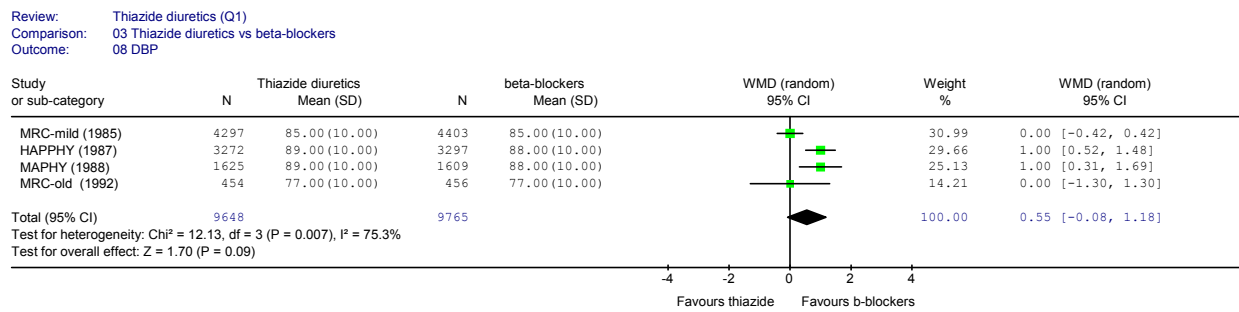
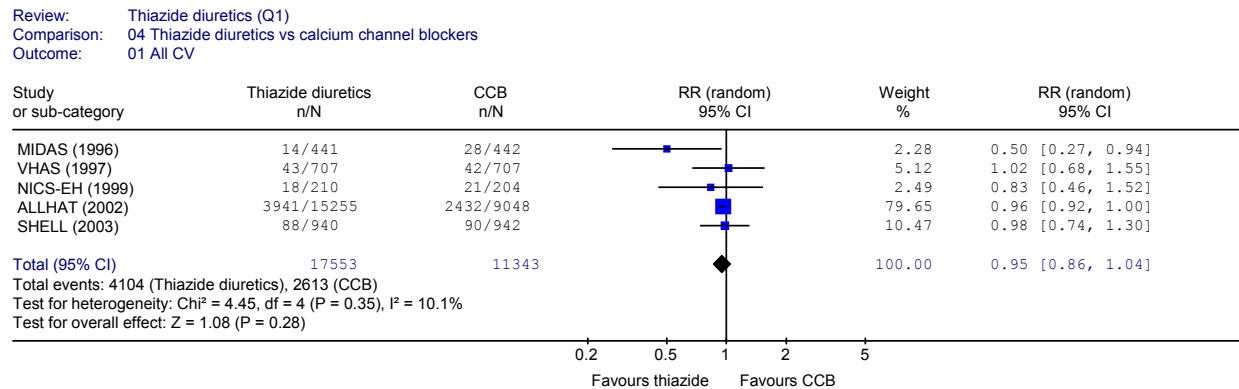


Figure 31: All cardiovascular events (thiazide diuretics versus CCB)



Review: Thiazide diuretics (Q1)
 Comparison: 04 Thiazide diuretics vs calcium channel blockers
 Outcome: 12 All CV (low versus high quality)

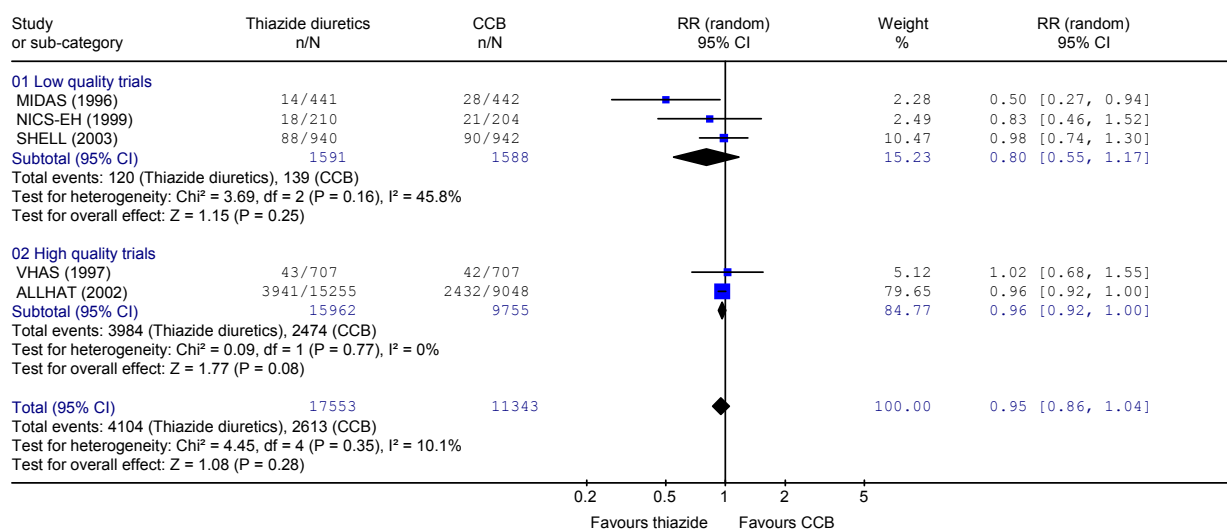


Figure 32: Coronary heart disease events (thiazide diuretics versus CCB)

Review: Thiazide diuretics (Q1)
 Comparison: 04 Thiazide diuretics vs calcium channel blockers
 Outcome: 02 CHD

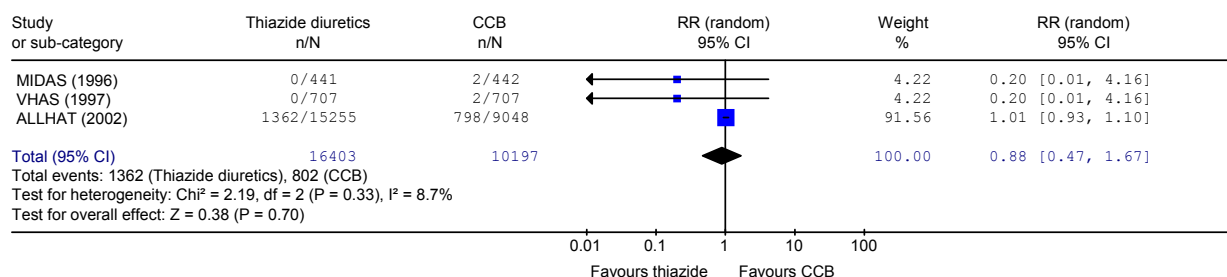


Figure 33: Myocardial infarction events (thiazide diuretics versus CCB)

Review: Thiazide diuretics (Q1)
 Comparison: 04 Thiazide diuretics vs calcium channel blockers
 Outcome: 03 MI

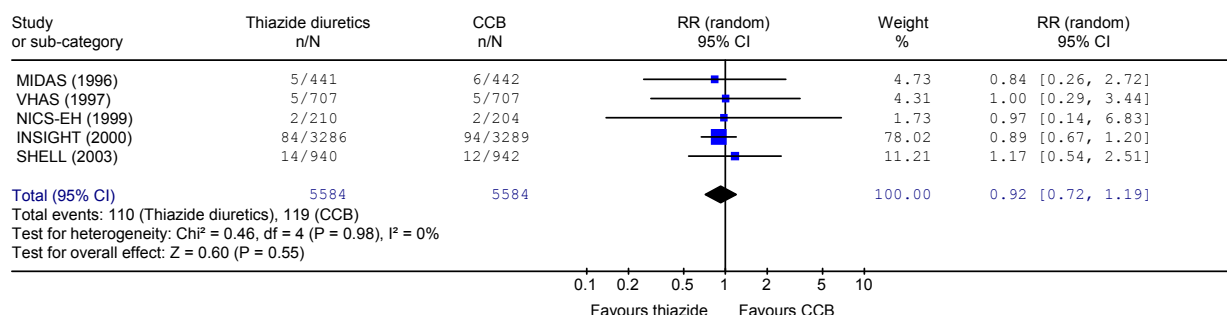


Figure 34: Heart failure events (thiazide diuretics versus CCB)

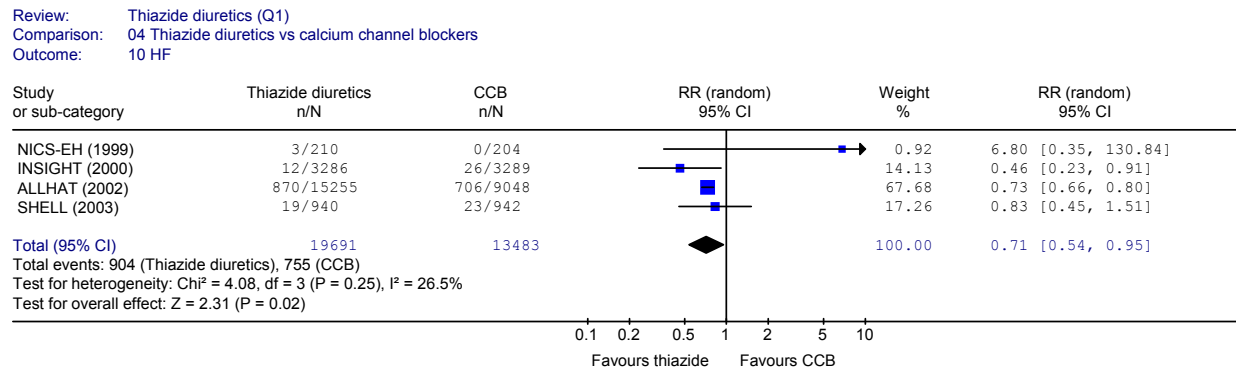


Figure 35: Stroke events (thiazide diuretics versus CCB)

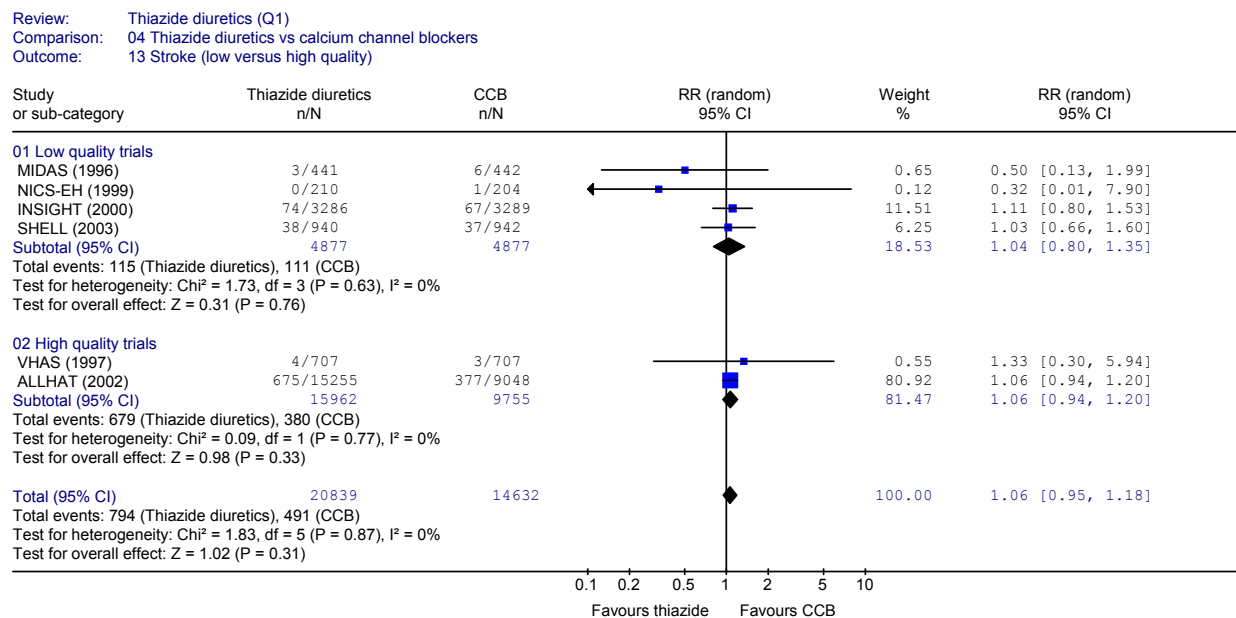
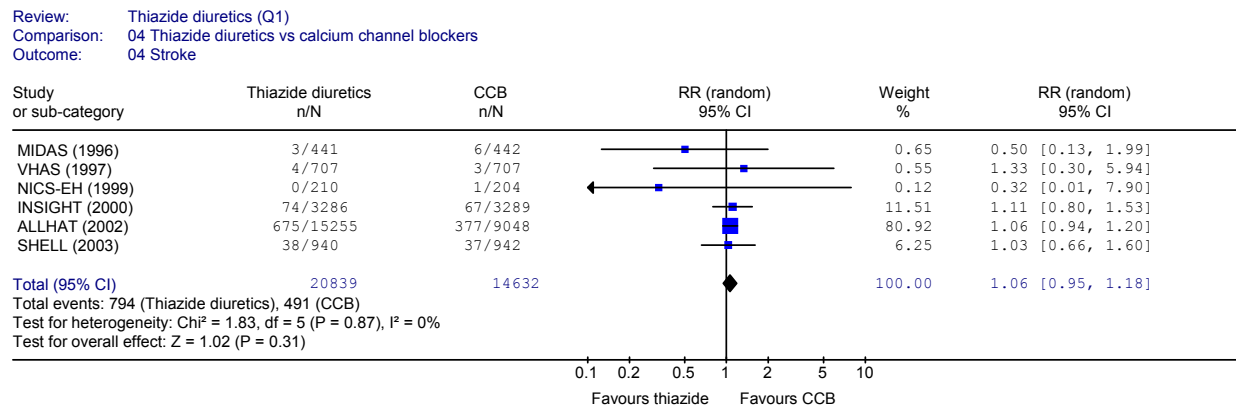


Figure 36: Cerebrovascular events (thiazide diuretics versus CCB)

Review: Thiazide diuretics (Q1)
Comparison: 04 Thiazide diuretics vs calcium channel blockers
Outcome: 05 CRV

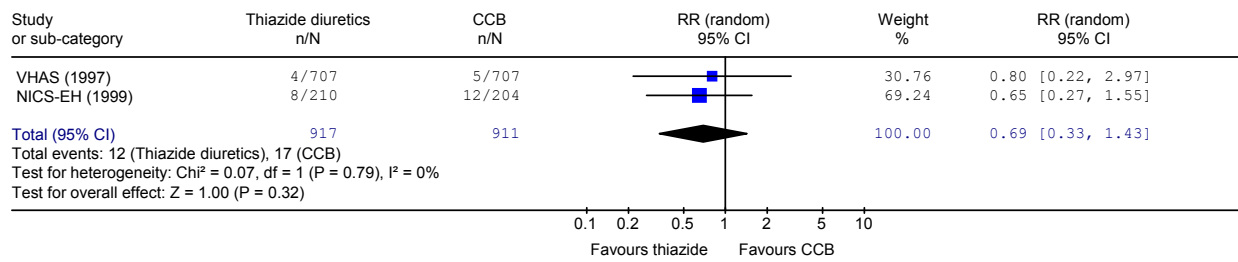


Figure 37: Renal failure (thiazide diuretics versus CCB)

Review: Thiazide diuretics (Q1)
Comparison: 04 Thiazide diuretics vs calcium channel blockers
Outcome: 11 RF

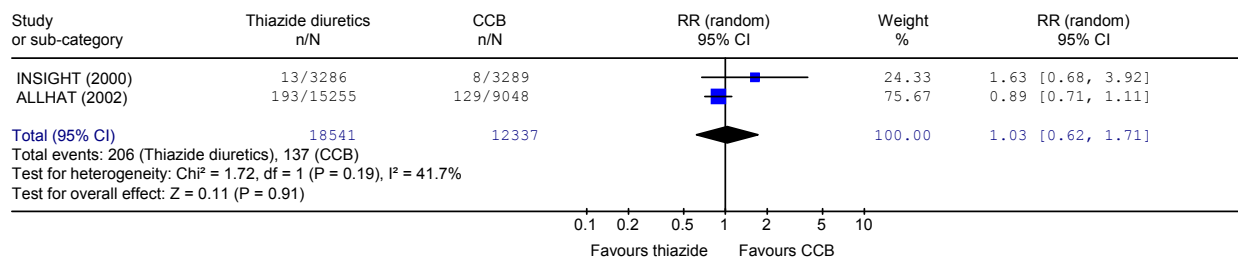
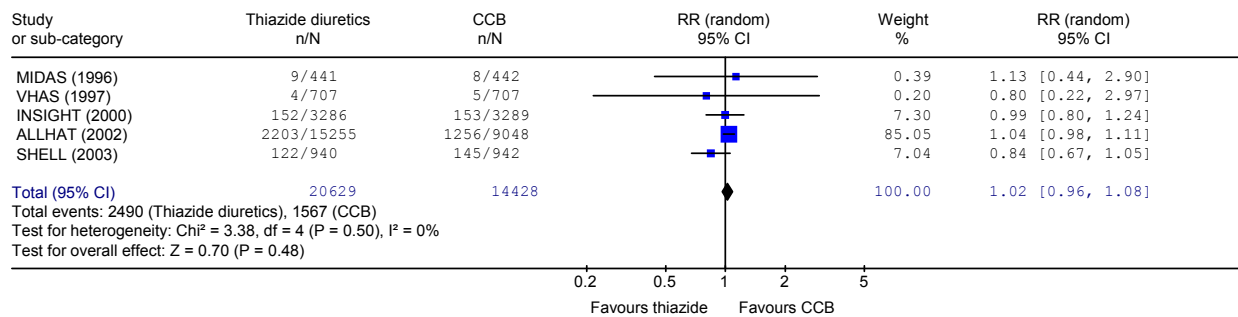


Figure 38: All deaths (thiazide diuretics versus CCB)

Review: Thiazide diuretics (Q1)
Comparison: 04 Thiazide diuretics vs calcium channel blockers
Outcome: 06 All death



Review: Thiazide diuretics (Q1)
Comparison: 04 Thiazide diuretics vs calcium channel blockers
Outcome: 14 All death (low versus high quality)

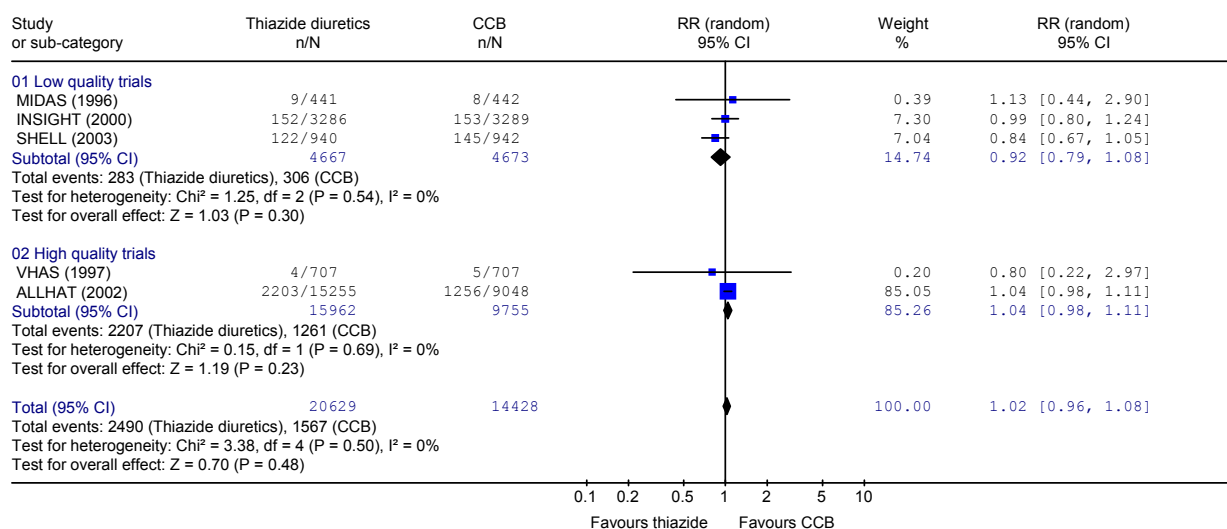


Figure 39: Withdrawals due to adverse events (thiazide diuretics versus CCB)

Review: Thiazide diuretics (Q1)
Comparison: 04 Thiazide diuretics vs calcium channel blockers
Outcome: 07 Withdraw

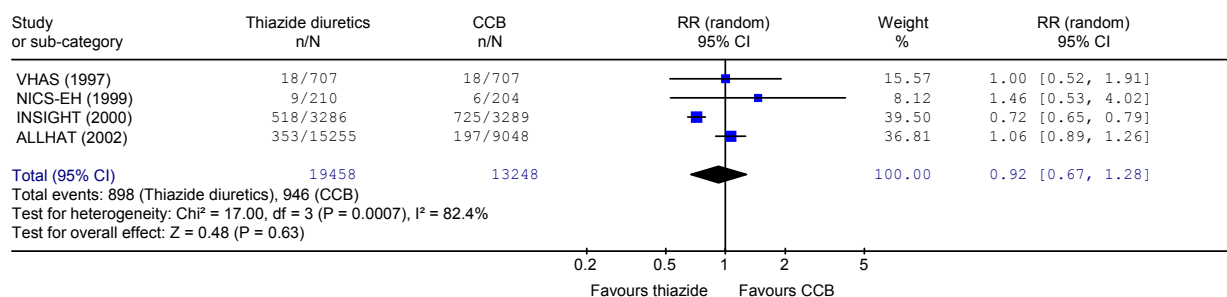


Figure 40: SBP (thiazide diuretics versus CCB)

Review: Thiazide diuretics (Q1)
Comparison: 04 Thiazide diuretics vs calcium channel blockers
Outcome: 08 SBP

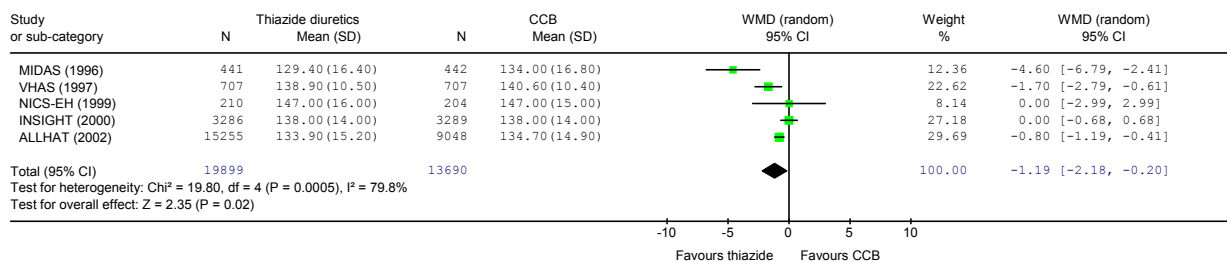


Figure 41: DBP (thiazide diuretics versus CCB)

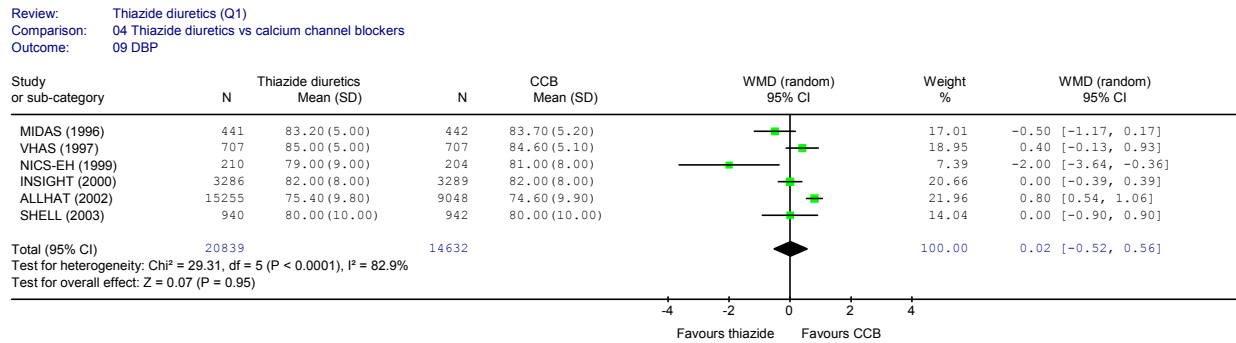


Figure 42: All deaths (moderate versus intensive lowering of BP)

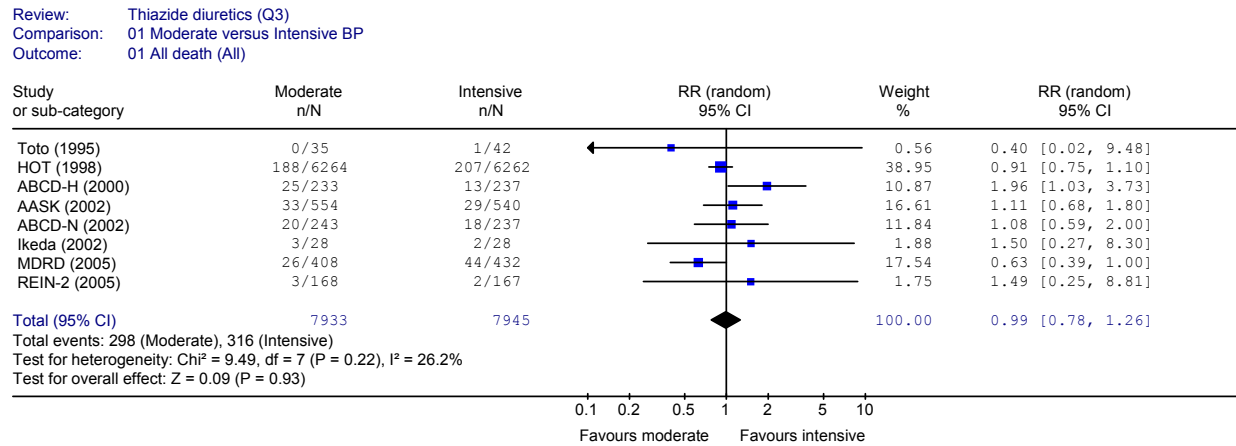


Figure 43: All deaths of chronic kidney disease patients (moderate versus intensive lowering of BP)

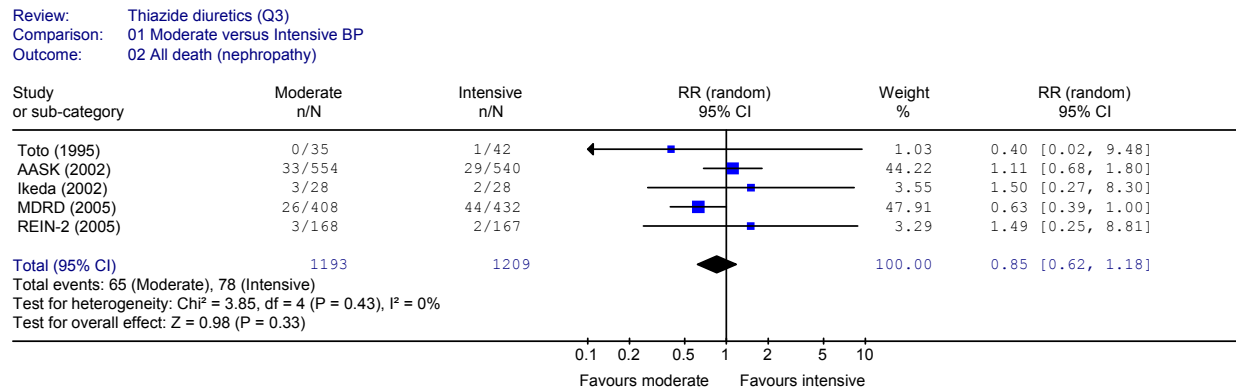


Figure 44: All deaths of diabetic patients (moderate versus intensive lowering of BP)

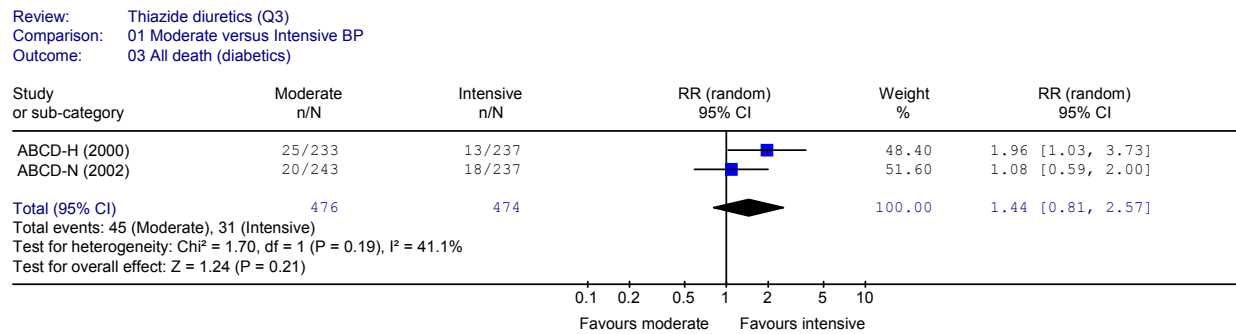


Figure 45: Cardiovascular deaths (moderate versus intensive lowering of BP)

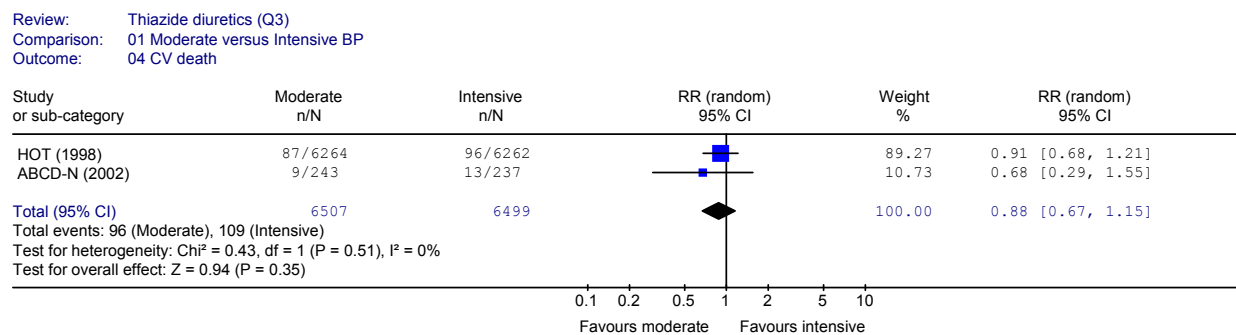


Figure 46: Stroke (moderate versus intensive lowering of BP)

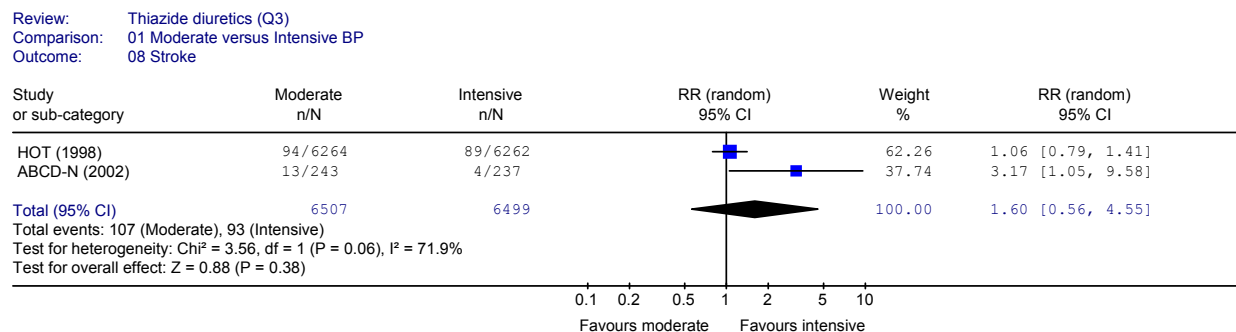


Figure 47: Myocardial infarction events (moderate versus intensive lowering of BP)

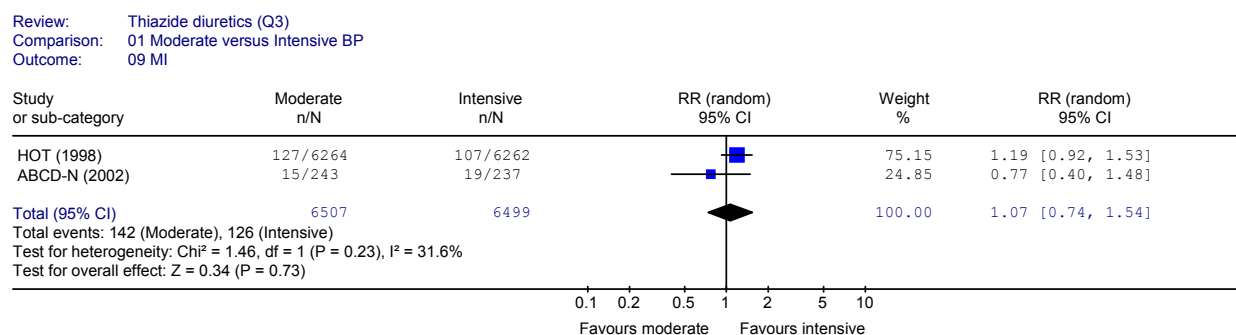


Figure 48: Renal failure (moderate versus intensive lowering of BP)

Review: Thiazide diuretics (Q3)
Comparison: 01 Moderate versus Intensive BP
Outcome: 05 RF

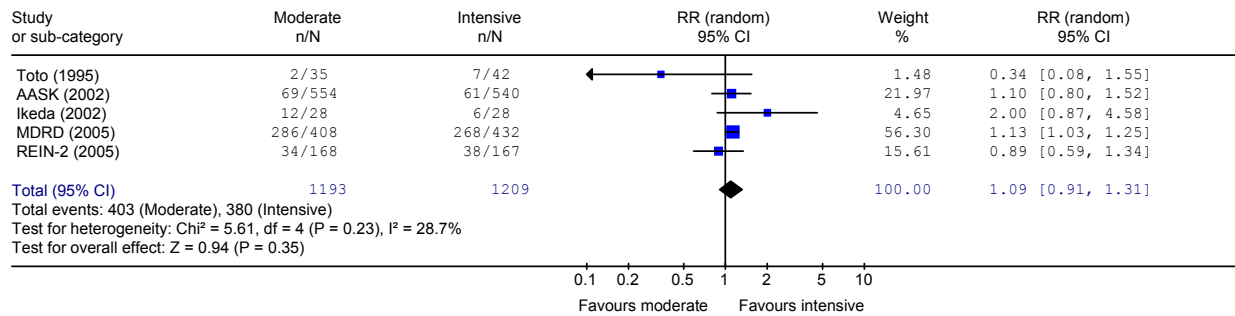


Figure 49: SBP (moderate versus intensive lowering of BP)

Review: Thiazide diuretics (Q3)
Comparison: 01 Moderate versus Intensive BP
Outcome: 06 SBP

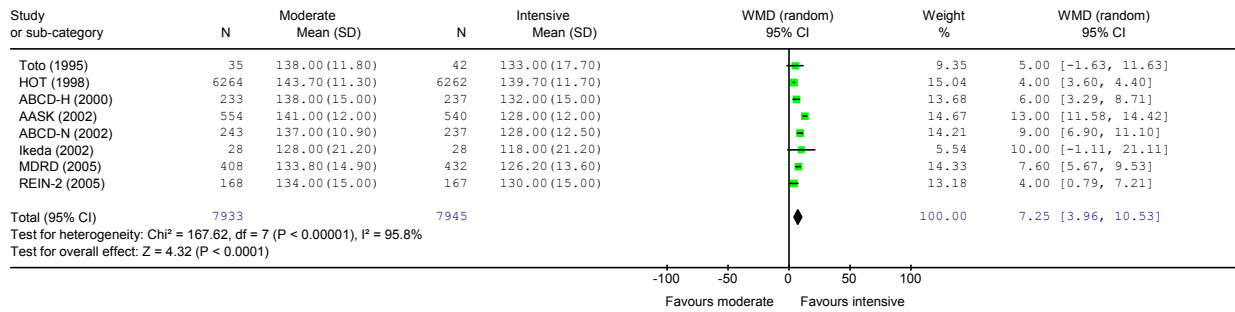


Figure 50: DBP (moderate versus intensive lowering of BP)

Review: Thiazide diuretics (Q3)
Comparison: 01 Moderate versus Intensive BP
Outcome: 07 DBP

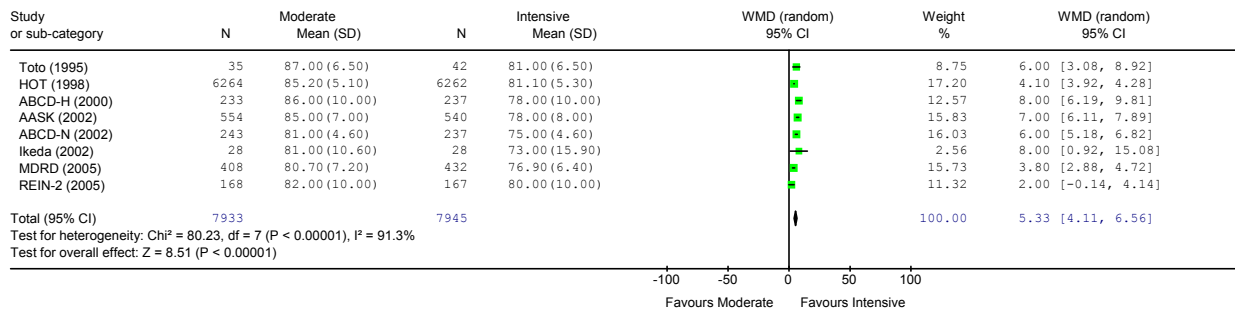


Figure 51: Selection of economic studies

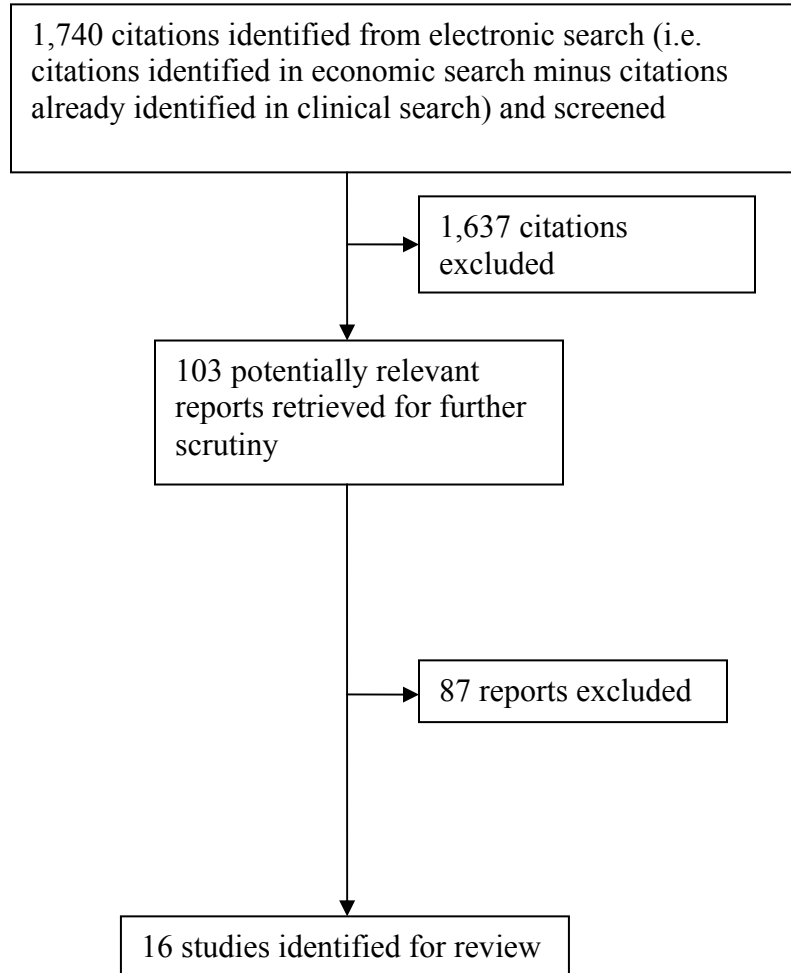
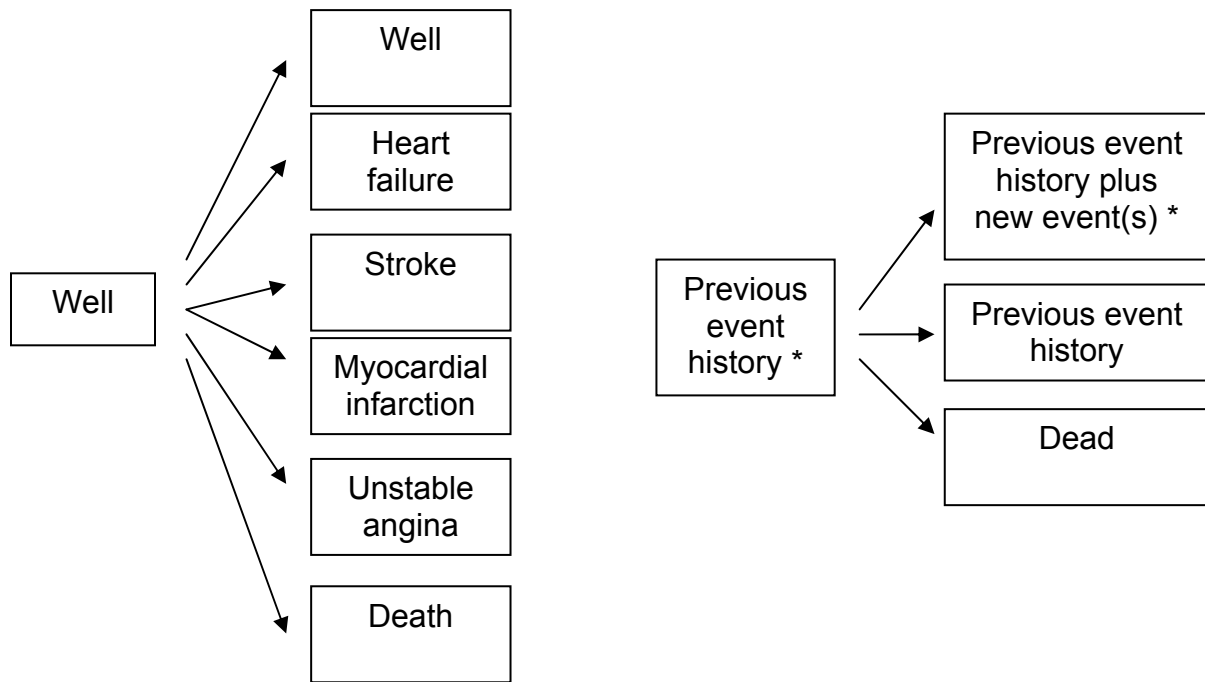


Figure 52: Simplified representation of Markov model

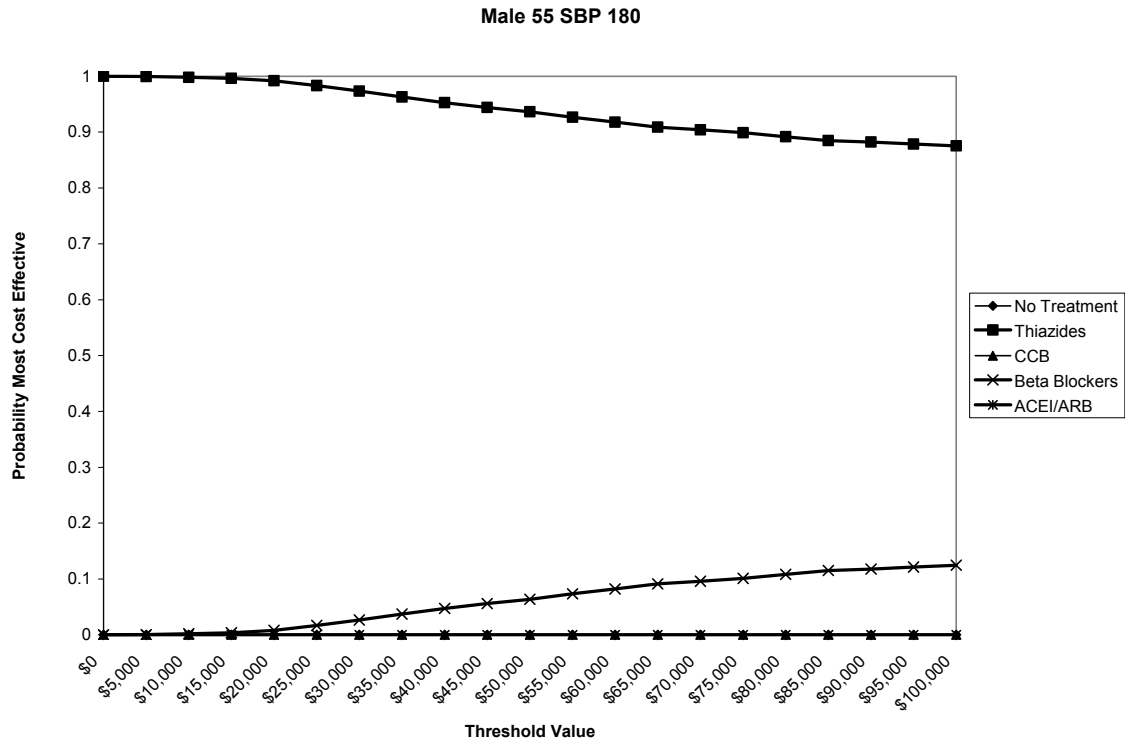
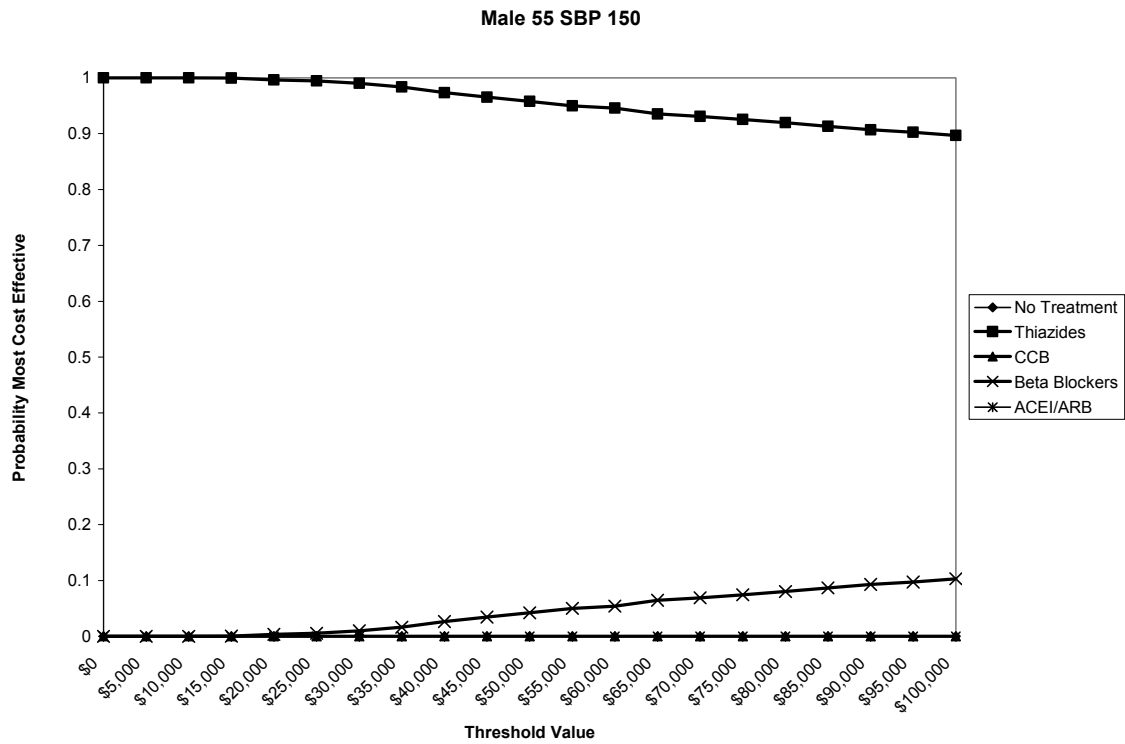


Transitions from “Well” states

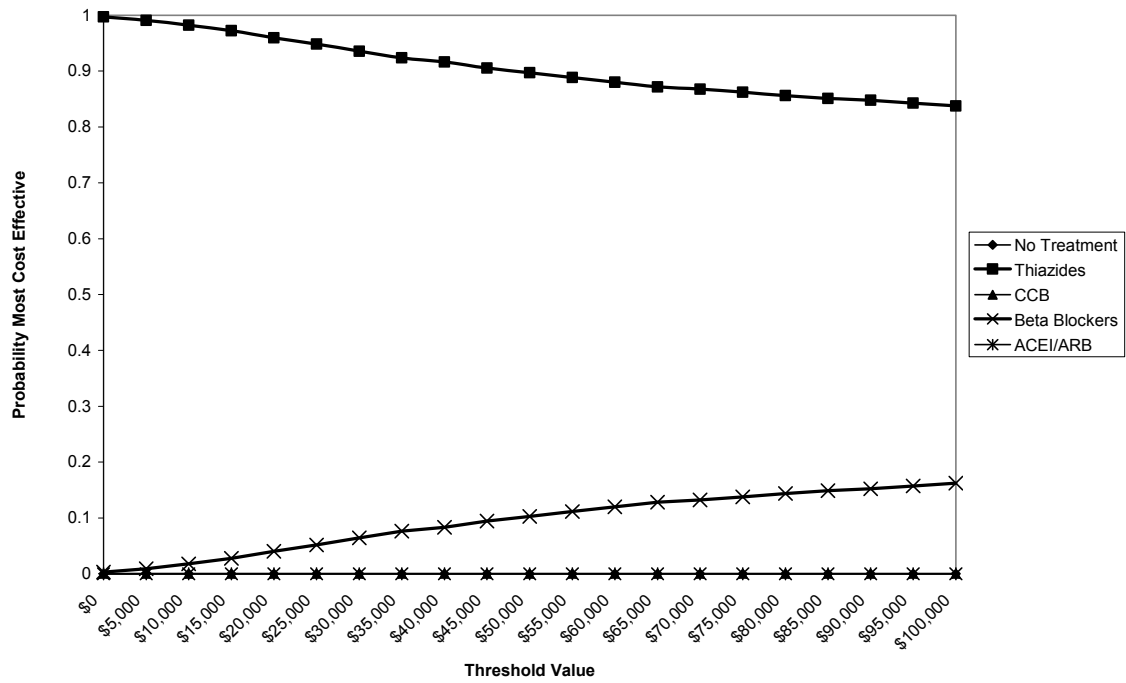
Transitions from previous events

*Previous event history relates to previous incidence of myocardial infarction, heart failure, stroke and/or angina. New event can be a different event(s) than in previous history or a repeat event(s).

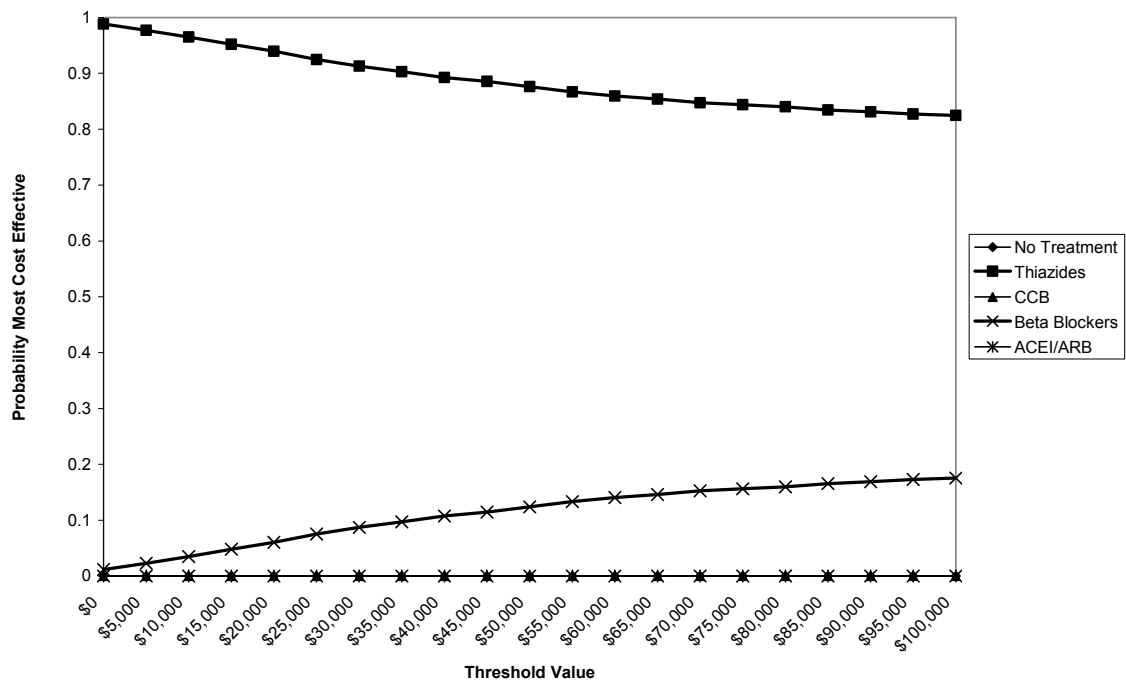
Figure 53: Cost effectiveness acceptability curves

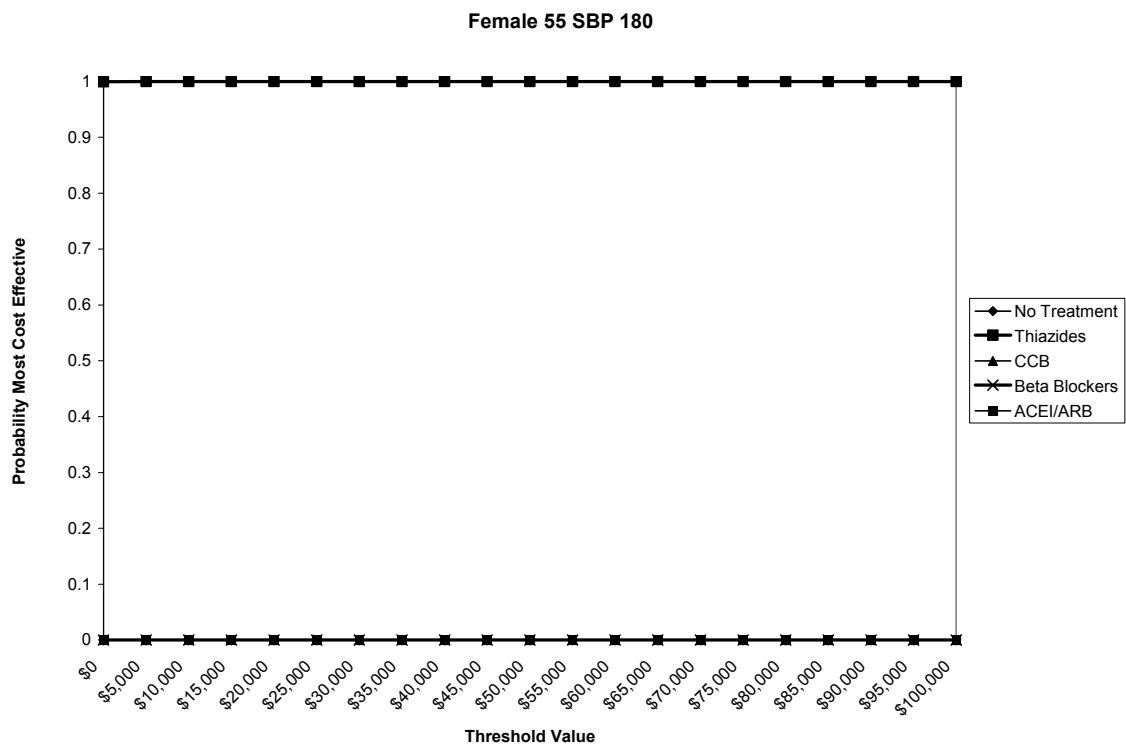
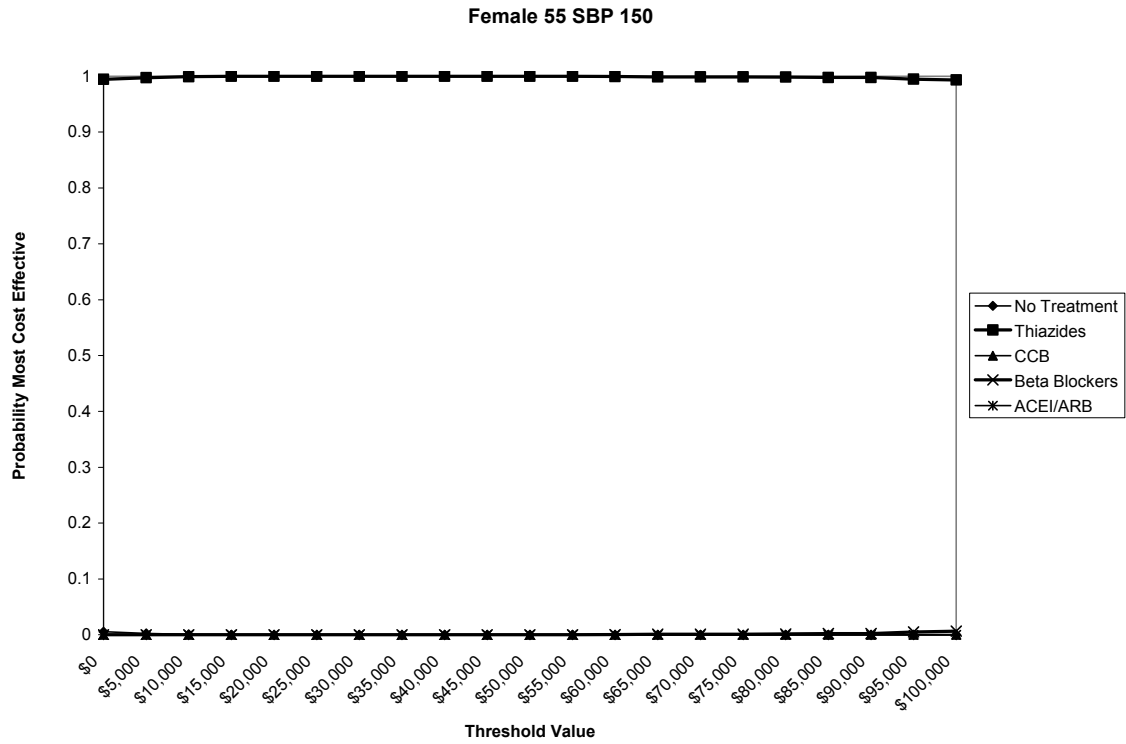


Male 65 SBP 150

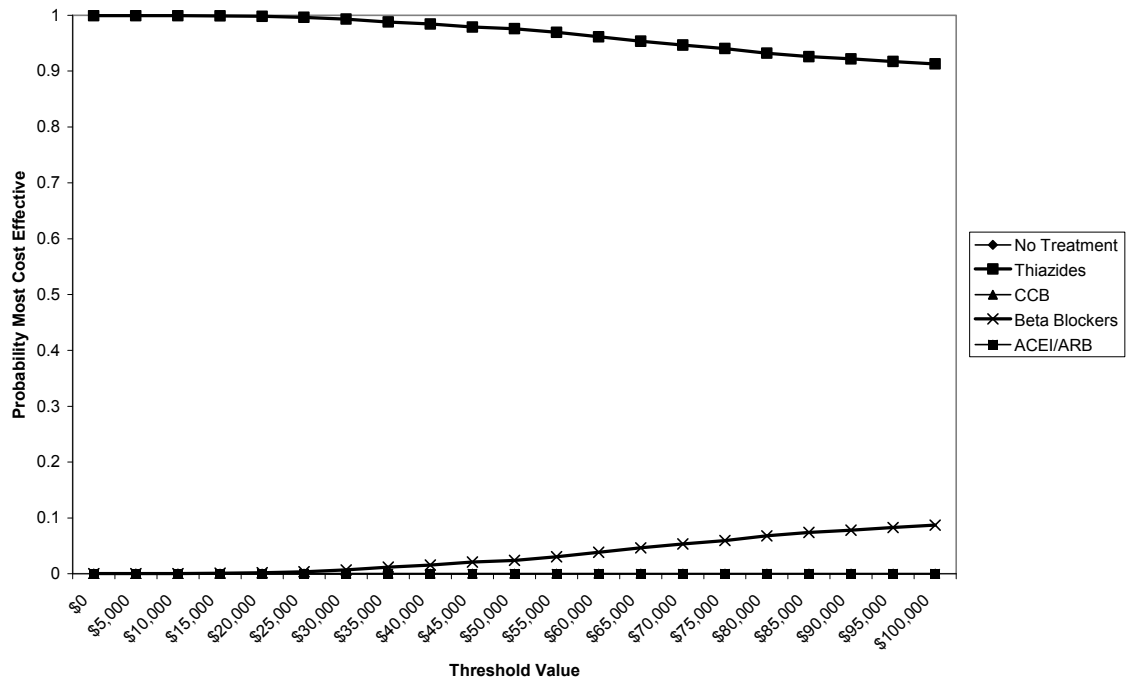


Male 65 SBP 180

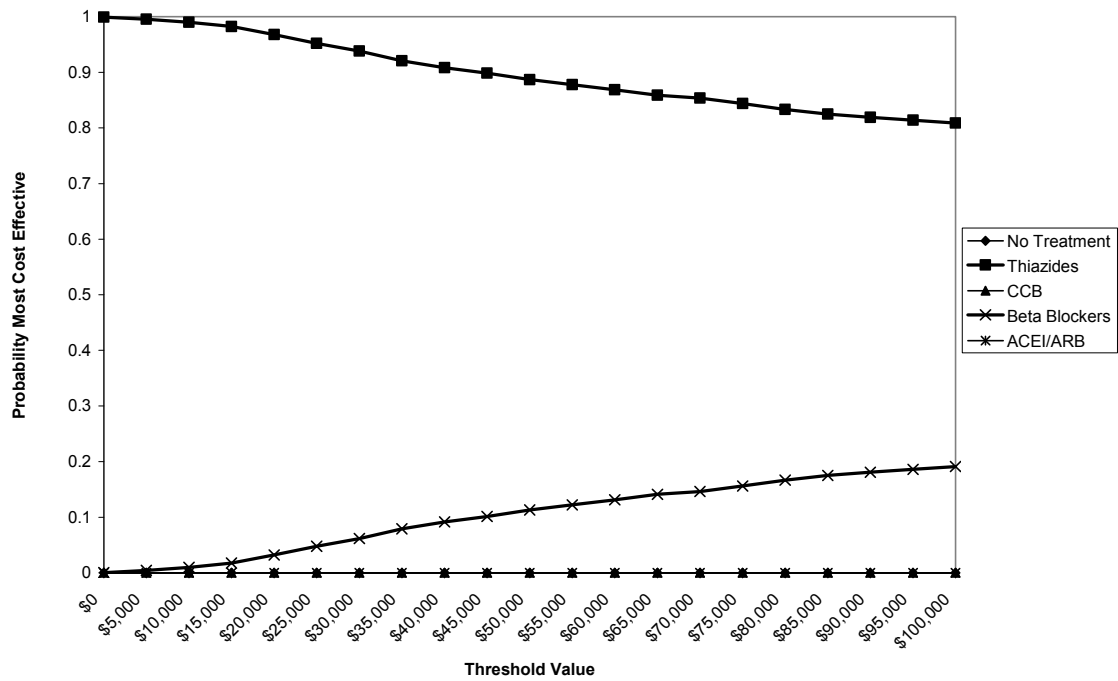




Female 65 SBP 150



Female 65 SBP 180



APPENDIX 1A: UTILIZATION DATA FOR SOME ANTIHYPERTENSIVE DRUG CLASSES FROM PROVINCIAL DRUG PROGRAMS IN PRINCE EDWARD ISLAND

Product	Category	2003/4	2004/5	2005/6	Mean
TZD	No. of persons (%)	1,531 (8.8)	1,644 (8.7)	1,862 (9.3)	1,679 (8.9)
	No. of prescriptions (%)	5,157 (7.2)	5,614 (7.2)	6,239 (7.8)	5,670 (7.4)
	Unit cost ¹	--	--	--	--
	Expenditure ² (%)	\$30,463 (0.7)	\$28,376 (0.6)	\$30,569 (0.6)	\$29,803 (0.6)
	Expenditure/person	20	17	16	18
α-blockers	No. of persons (%)	75 (0.4)	77 (0.4)	87 (0.4)	80 (0.4)
	No. of prescriptions (%)	302 (0.4)	339 (0.4)	368 (0.5)	336 (0.4)
	Unit cost	--	--	--	--
	Expenditure (%)	\$8,949 (0.2)	\$8,557 (0.2)	\$8,553 (0.2)	\$8,686 (0.2)
	Expenditure/person	119	111	98	109
β-blockers	No. of persons (%)	4,496 (25.8)	4,832 (25.6)	5,050 (25.2)	4,793 (25.5)
	No. of prescriptions (%)	17,962 (24.9)	19,438 (24.8)	20,646 (25.8)	19,349 (25.2)
	Unit cost	--	--	--	--
	Expenditure (%)	\$400,234 (9.3)	\$414,880 (8.7)	\$440,124 (8.6)	\$418,413 (8.9)
	Expenditure/person	89	86	87	87
ACEI	No. of persons (%)	5,021 (28.8)	5,309 (28.1)	5,571 (27.8)	5,300 (28.2)
	No. of prescriptions (%)	21,943 (30.5)	23,460 (29.9)	20,929 (26.2)	22,111 (28.9)
	Unit cost	--	--	--	--
	Expenditure (%)	\$1,599,140 (37.1)	\$1,688,168 (35.5)	\$1,766,958 (34.4)	\$1,684,755 (35.7)
	Expenditure/person	318	318	317	318
ACEI + TZD	No. of persons (%)	37 (0.2)	63 (0.3)	80 (0.4)	60 (0.3)
	No. of prescriptions (%)	139 (0.2)	269 (0.3)	325 (0.4)	244 (0.3)
	Unit cost	--	--	--	--
	Expenditure (%)	\$6,264 (0.2)	\$13,053 (0.3)	\$19,417 (0.4)	\$12,911 (0.3)
	Expenditure/person	169	207	243	206
ARB	No. of persons (%)	1,509 (8.7)	1,741 (9.2)	1,977 (9.9)	1,742 (9.3)
	No. of prescriptions (%)	6,74 (8.7)	7,198 (9.2)	8,332 (10.4)	7,268 (9.4)
	Unit cost	--	--	--	--
	Expenditure (%)	\$462,778 (10.7)	\$560,318 (11.8)	\$662,522 (12.9)	\$561,873 (11.8)
	Expenditure/person	307	322	335	321
ARB + TZD	No. of persons (%)	181 (1.0)	283 (1.5)	378 (1.9)	281 (1.5)
	No. of prescriptions (%)	666 (0.9)	1,059 (1.4)	1,447 (1.8)	1,057 (1.4)
	Unit cost	--	--	--	--
	Expenditure (%)	\$37,855 (0.9)	\$74,455 (1.6)	\$110,737 (2.2)	\$74,349 (1.6)
	Expenditure/person	209	263	293	255

Product	Category	2003/4	2004/5	2005/6	Mean
CCB	No. of persons (%)	4,604 (26.4)	4,951 (26.2)	5,027 (25.1)	4,861 (25.9)
	No. of prescriptions (%)	19,586 (27.2)	20,975 (26.8)	21,699 (27.1)	20,753 (27.0)
	Unit cost	--	--	--	--
	Expenditure (%)	\$1,763,120 (40.9)	\$1,962,926 (41.3)	\$2,102,750 (40.9)	\$1,942,932 (41.0)
	Expenditure/person	383	396	418	399
Total	No. of persons (%)	17,454 (100)	18,900 (100)	20,032 (100)	18,795 (100)
	No. of prescriptions (%)	72,079 (100)	78,352 (100)	79,985 (100)	76,805 (100)
	Expenditure (%)	\$4,308,803 (100)	\$4,750,733 (100)	\$5,141,630(100)	\$4,733,722 (100)

TZD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers

¹, indicates average unit cost

², indicates drug cost plus markup cost plus dispensing fee minus beneficiary contribution

Data obtained from Prince Edward Island Ministry of Health (Patrick Crawford, Prince Edward Island Drug Programs, Department of Social Services and Seniors: personal communication, 2007 Mar 5).

APPENDIX 1B: UTILIZATION DATA FOR SOME ANTIHYPERTENSIVE DRUG CLASSES FROM PROVINCIAL DRUG PROGRAMS IN NEW BRUNSWICK

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
TZD	No. of persons (%)	15,086 (18.1)	16,437 (18.2)	17,330 (18.3)	19,198 (19.1)	20,292 (19.1)	21,115 (19.0)	18,243 (18.7)
	No. of prescriptions (%)	65,225 (16.5)	70,898 (16.7)	75,053 (16.8)	83,692 (17.7)	88,845 (18.0)	92,433 (17.9)	79,358 (17.3)
	Unit cost ¹	\$0.11	\$0.12	\$0.13	\$0.13	\$0.13	\$0.13	\$0.13
	Expenditure ² (%)	\$293,563 (1.9)	\$359,003 (2.0)	\$410,812 (2.1)	\$454,484 (2.2)	\$480,453 (2.1)	\$497,702 (2.1)	\$416,003 (2.1)
	Expenditure/person	\$19	\$19	\$24	\$24	\$24	\$24	\$22
α-blockers	No. of persons (%)	1,773 (2.1)	1,854 (2.1)	1,815 (1.9)	2,051 (2.0)	2,136 (2.0)	2,271 (2.0)	1,983 (2.0)
	No. of prescriptions (%)	7,197 (1.8)	8,021 (1.9)	7,970 (1.8)	8,583 (1.8)	8,941 (1.8)	9,746 (1.9)	8,410 (1.8)
	Unit cost	\$0.44	\$0.43	\$0.42	\$0.43	\$0.43	\$0.43	\$0.43
	Expenditure (%)	\$201,293 (1.3)	\$234,977 (1.3)	\$239,444 (1.2)	\$264,056 (1.3)	\$283,493 (1.3)	\$308,424 (1.3)	\$255,281 (1.3)
	Expenditure/person	\$114	\$127	\$132	\$129	\$133	\$136	\$129
β-blockers	No. of persons (%)	18,600 (22.3)	19,474 (21.6)	20,636 (21.8)	22,183 (22.1)	23,875 (22.5)	24,916 (22.4)	21,614 (22.1)
	No. of prescriptions (%)	93,483 (23.6)	97,268 (22.9)	101,813 (22.8)	108,853 (23.0)	114,522 (23.2)	119,115 (23.1)	105,842 (23.1)
	Unit cost	\$0.46	\$0.47	\$0.46	\$0.43	\$0.37	\$0.37	\$0.43
	Expenditure (%)	\$2,013,690 (12.7)	\$2,275,756 (12.8)	\$2,369,649 (12.3)	\$2,554,936 (12.2)	\$2,600,809 (11.6)	\$2,736,997 (11.4)	\$2,425,306 (12.1)
	Expenditure/person	\$108	\$117	\$115	\$115	\$109	\$110	\$112
β-blockers + TZD	No. of persons (%)	605 (0.7)	577 (0.6)	534 (0.6)	512 (0.5)	478 (0.4)	460 (0.4)	528 (0.5)
	No. of prescriptions (%)	3,035 (0.8)	2,762 (0.6)	2,484 (0.6)	2,390 (0.5)	2,169 (0.4)	2,057 (0.4)	2,483 (0.5)
	Unit cost	\$0.80	\$0.80	\$0.80	\$0.80	\$0.75	\$0.68	\$0.77
	Expenditure (%)	\$130,156 (0.8)	\$126,459 (0.7)	\$117,659 (0.6)	\$116,962 (0.6)	\$97,191 (0.4)	\$78,084 (0.3)	\$111,085 (0.6)
	Expenditure/person	\$215	\$219	\$220	\$228	\$203	\$170	\$209
ACEI	No. of persons (%)	25,168 (30.2)	27,855 (30.8)	28,516 (30.1)	29,209 (29.1)	30,316 (28.5)	31,445 (28.3)	28,752 (29.4)
	No. of prescriptions (%)	117,111 (29.6)	128,988 (30.3)	134,372 (30.1)	138,563 (29.3)	142,443 (28.9)	148,589 (28.8)	135,011 (29.4)
	Unit cost	\$0.78	\$0.77	\$0.78	\$0.79	\$0.78	\$0.77	\$0.78
	Expenditure (%)	\$6,553,888	\$7,395,286	\$7,984,214	\$8,541,349	\$8,971,265	\$9,368,967	\$8,135,828

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
		(41.5)	(41.5)	(41.3)	(40.7)	(40.0)	(39.0)	(40.5)
	Expenditure/person	\$260	\$265	\$280	\$292	\$296	\$298	\$282
ACEI + TZD	No. of persons (%)	265 (0.3)	300 (0.3)	314 (0.3)	357 (0.4)	383 (0.4)	548 (0.5)	361 (0.4)
	No. of prescriptions (%)	1451 (0.4)	1527 (0.4)	1521 (0.3)	1687 (0.4)	1864 (0.4)	2337 (0.5)	1731 (0.4)
	Unit cost ¹	\$0.92	\$0.91	0.91	\$0.92	\$0.94	\$0.94	\$0.92
	Expenditure ² (%)	\$81,878 (0.5)	\$88,988 (0.5)	\$93,782 (0.5)	\$108,601 (0.5)	\$122,338 (0.5)	\$152,617 (0.6)	\$108,034 (0.5)
	Expenditure/person	\$309	\$297	\$299	\$304	\$319	\$278	\$301
ARB	No. of persons (%)	1,675 (2.0)	2,389 (2.6)	3,387 (3.6)	4,034 (4.0)	5,352 (5.0)	6,129 (5.5)	3,828 (3.9)
	No. of prescriptions (%)	8,384 (2.1)	11,941 (2.8)	16,236 (3.6)	19,503 (4.1)	22,639 (4.6)	27,160 (5.3)	17,644 (3.8)
	Unit cost	\$1.12	\$1.08	\$1.06	\$1.10	\$1.12	\$1.12	\$1.10
	Expenditure (%)	\$469,094 (3.0)	\$724,566 (4.1)	\$1,028,023 (5.3)	\$1,307,735 (6.2)	\$1,622,307 (7.2)	\$2,025,222 (8.4)	\$1,196,158 (6.0)
	Expenditure/person	\$280	\$303	\$304	\$324	\$303	\$330	\$307
ARB + TZD	No. of persons (%)	104 (0.1)	191 (0.2)	336 (0.4)	492 (0.5)	598 (0.6)	948 (0.9)	445 (0.5)
	No. of prescriptions (%)	494 (0.1)	958 (0.2)	1553 (0.3)	2326 (0.5)	2900 (0.6)	3814 (0.7)	2008 (0.4)
	Unit cost	\$1.16	\$1.13	\$1.13	\$1.13	\$1.15	\$1.17	\$1.15
	Expenditure (%)	\$30,028 (0.2)	\$57,757 (0.3)	\$96,827 (0.5)	\$152,634 (0.7)	\$204,873 (0.9)	\$284,978 (1.2)	\$137,850 (0.7)
	Expenditure/person	\$289	\$302	\$288	\$310	\$343	\$301	\$306
CCB	No. of persons (%)	20,048 (24.1)	21,289 (23.6)	21,765 (23.0)	22,331 (22.2)	22,906 (21.5)	23,453 (21.1)	21,965 (22.5)
	No. of prescriptions (%)	99,714 (25.2)	103,165 (24.2)	105,537 (23.6)	107,544 (22.7)	108,721 (22.1)	111,317 (21.5)	106,000 (23.1)
	Unit cost	\$0.92	\$0.90	\$0.89	\$0.90	\$0.90	\$0.96	\$0.91
	Expenditure (%)	\$6,037,157 (38.2)	\$6,553,644 (36.8)	\$6,980,028 (36.1)	\$7,500,466 (35.7)	\$8,031,792 (35.8)	\$8,595,317 (35.7)	\$7,283,067 (36.3)
	Expenditure/person	\$301	\$308	\$321	\$336	\$351	\$366	\$331
Total	No. of persons (%)	83,324 (100)	90,366 (100)	94,633 (100)	100,367 (100)	106,336 (100)	111,285 (100)	97,719 (100)
	No. of prescriptions (%)	396,094 (100)	425,528 (100)	446,539 (100)	473,114 (100)	493,044 (100)	516,568 (100)	458,481 (100)
	Expenditure (%)	\$15,810,747 (100)	\$17,816,437 (100)	\$19,320,438 (100)	\$21,001,187 (100)	\$22,414,522 (100)	\$24,048,309 (100)	\$20,068,607 (100)

TZD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers

¹, indicates average unit cost

², indicates drug cost plus markup cost plus dispensing fee minus beneficiary contribution

Data obtained from New Brunswick Ministry of Health (Brenda Currie, New Brunswick Prescription Drug Program: personal communication, 2007 Mar 15).

APPENDIX 1C: UTILIZATION DATA FOR SOME ANTIHYPERTENSIVE DRUG CLASSES FROM PROVINCIAL DRUG PROGRAMS IN BRITISH COLUMBIA

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
TZD	No. of persons (%)	130,624 (25.1)	135,334 (23.8)	101,809 (18.7)	135,815 (24.5)	145,742 (25.0)	148,122 (24.7)	132,908 (23.7)
	No. of prescriptions (%)	428,083 (22.6)	424,786 (20.2)	340,230 (16.1)	494,506 (22.2)	594,374 (22.5)	656,862 (22.2)	489,807 (21.1)
	Unit cost ¹	\$0.13	\$0.12	\$0.13	\$0.13	\$0.13	\$0.13	\$0.13
	Expenditure ² (%)	\$1,986,686 (2.3)	\$2,182,794 (2.3)	\$2,733,412 (2.8)	\$4,543,765 (5.1)	\$5,422,976 (5.4)	\$5,865,398 (5.4)	\$3,789,172 (3.9)
	Expenditure/person	\$15	\$16	\$27	\$33	\$37	\$40	\$28
α-blockers	No. of persons (%)	4,707 (0.9)	4,268 (0.8)	3,817 (0.7)	3,228 (0.6)	3,061 (0.5)	2,859 (0.5)	3,657 (0.7)
	No. of prescriptions (%)	15,650 (0.8)	14,563 (0.7)	13,662 (0.6)	11,034 (0.5)	11,661 (0.4)	12,084 (0.4)	13,109 (0.6)
	Unit cost	\$0.37	\$0.36	\$0.35	\$0.35	\$0.35	\$0.34	\$0.35
	Expenditure (%)	\$658,297 (0.8)	\$568,546 (0.6)	\$495,143 (0.5)	\$386,480 (0.4)	\$407,132 (0.4)	\$400,007 (0.4)	\$485,934 (0.5)
	Expenditure/person	\$140	\$133	\$130	\$120	\$133	\$140	\$133
β-blockers	No. of persons (%)	124,253 (23.9)	131,150 (23.1)	124,057 (22.8)	120,691 (21.8)	124,766 (21.4)	125,188 (20.8)	125,018 (22.3)
	No. of prescriptions (%)	464,970 (24.6)	493,616 (23.5)	487,009 (23.0)	501,423 (22.5)	583,682 (22.1)	644,731 (21.8)	529,239 (22.8)
	Unit cost	\$0.51	\$0.51	\$0.51	\$0.51	\$0.51	\$0.48	\$0.51
	Expenditure (%)	\$12,000,111 (14.2)	\$12,114,560 (12.7)	\$11,214,171 (11.4)	\$11,475,621 (12.8)	\$12,792,200 (12.6)	\$12,972,628 (12.0)	\$12,094,88 2 (12.6)
	Expenditure/person	\$97	\$92	\$90	\$95	\$103	\$104	\$97
β-blockers + TZD	No. of persons (%)	688 (0.1)	641 (0.1)	581 (0.1)	476 (0.1)	441 (0.1)	412 (0.1)	540 (0.1)
	No. of prescriptions (%)	2,300 (0.1)	2,096 (0.1)	1,952 (0.1)	1,484 (0.1)	1,481 (0.1)	1,390 (0.1)	1,784 (0.1)
	Unit cost	\$0.74	\$0.75	\$0.74	\$0.75	\$0.76	\$0.78	\$0.75
	Expenditure (%)	\$145,102 (0.1)	\$129,814 (0.1)	\$107,703 (0.1)	\$81,957 (0.1)	\$79,671 (0.1)	\$80,189 (0.1)	\$104,073 (0.1)
	Expenditure/person	\$211	\$203	\$185	\$172	\$181	\$195	\$191

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
ACEI	No. of persons (%)	137,784 (26.5)	160,138 (28.2)	168,227 (31.0)	154,342 (27.8)	160,319 (27.5)	165,455 (27.6)	157,711 (28.1)
	No. of prescriptions (%)	519,796 (27.5)	628,388 (29.9)	688,694 (32.5)	653,851 (29.3)	764,961 (29.0)	859,708 (29.1)	685,900 (29.5)
	Unit cost	\$0.78	\$0.78	\$0.79	\$0.80	\$0.79	\$0.77	\$0.79
	Expenditure (%)	\$33,689,330 (39.7)	\$39,754,829 (41.8)	\$41,985,273 (42.5)	\$35,973,120 (40.2)	\$40,046,082 (39.5)	\$42,216,122 (39.1)	\$38,944,126 (40.5)
	Expenditure/person	\$245	\$248	\$250	\$233	\$250	\$255	\$247
ACEI + TZD	No. of persons (%)	1,546 (0.3)	2,355 (0.4)	3,146 (0.6)	3,694 (0.7)	4,492 (0.8)	5,221 (0.9)	3,409 (0.6)
	No. of prescriptions (%)	4,590 (0.2)	7,442 (0.4)	10,031 (0.5)	11,489 (0.5)	15,962 (0.6)	19,938 (0.7)	11,575 (0.5)
	Unit cost	\$0.88	\$0.88	\$0.88	\$0.90	\$0.96	\$0.91	\$0.90
	Expenditure (%)	\$297,130 (0.4)	\$485,336 (0.5)	\$647,119 (0.7)	\$710,833 (0.8)	\$968,909 (1.0)	\$1,147,531 (1.1)	\$709,476 (0.7)
	Expenditure/person	\$192	\$206	\$206	\$192	\$216	\$220	\$205
ARB	No. of persons (%)	9,603 (1.8)	14,526 (2.6)	18,522 (3.4)	20,226 (3.6)	23,402 (4.0)	26,173 (4.4)	18,742 (3.3)
	No. of prescriptions (%)	33,305 (1.8)	53,392 (2.5)	71,360 (3.4)	77,515 (3.5)	101,219 (3.8)	124,499 (4.2)	76,882 (3.3)
	Unit cost	\$1.14	\$1.14	\$1.14	\$1.14	\$1.15	\$1.17	\$1.15
	Expenditure (%)	\$2,998,119 (3.5)	\$4,638,297 (4.9)	\$5,896,994 (6.0)	\$5,554,537 (6.2)	\$6,954,013 (6.9)	\$8,119,119 (7.5)	\$5,693,513 (5.9)
	Expenditure/person	\$312	\$319	\$318	\$275	\$297	\$310	\$305
ARB + TZD	No. of persons (%)	1,143 (0.2)	2,104 (0.4)	3,585 (0.7)	4,737 (0.9)	6,194 (1.1)	7,338 (1.2)	4,184 (0.7)
	No. of prescriptions (%)	3,610 (0.2)	6,256 (0.3)	10,928 (0.5)	14,313 (0.6)	21,588 (0.8)	27,521 (0.9)	14,036 (0.6)
	Unit cost	\$1.14	\$1.14	\$1.15	\$1.15	\$1.17	\$1.18	\$1.16
	Expenditure (%)	\$361,737 (0.2)	\$596,207 (0.6)	\$975,888 (1.0)	\$1,154,552 (1.3)	\$1,681,867 (1.7)	\$2,091,599 (1.9)	\$1,143,642 (1.2)
	Expenditure/person	\$316	\$283	\$272	\$244	\$272	\$285	\$279
CCB	No. of persons (%)	110,136	118,055	119,435 (22.0)	111,300 (20.1)	115,360	119,669	115,659

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
		(21.2)	(20.8)			(19.8)	(19.9)	(20.6)
	No. of prescriptions (%)	420,533 (22.2)	468,718 (22.3)	495,482 (23.4)	464,817 (20.8)	541,120 (20.5)	612,558 (20.7)	500,538 (21.5)
	Unit cost	\$1.03	\$1.04	\$1.05	\$1.07	\$1.09	\$1.09	\$1.06
	Expenditure (%)	\$32,646,380 (38.5)	\$34,548,740 (36.4)	\$34,705,347 (35.1)	\$29,529,332 (33.0)	\$33,006,017 (32.6)	\$35,118,731 (32.5)	\$33,259,091 (34.6)
	Expenditure/person	\$296	\$293	\$291	\$265	\$286	\$293	\$287
Total	No. of persons (%)	520,484 (100)	568,571 (100)	543,179 (100)	554,509 (100)	583,777 (100)	600,437 (100)	561,826 (100)
	No. of prescriptions (%)	1,892,837 (100)	2,099,257 (100)	2,119,348 (100)	2,230,432 (100)	2,636,048 (100)	2,959,291 (100)	2,322,869 (100)
	Expenditure (%)	\$84,782,894 (100)	\$95,019,121 (100)	\$98,761,049 (100)	\$89,410,197 (100)	\$101,358,868 (100)	\$108,011,325 (100)	\$96,223,909 (100)

TZD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers

1, indicates average unit cost

2, indicates drug cost plus markup cost plus dispensing fee minus beneficiary contribution

Data obtained from British Columbia Ministry of Health (Brett Wilmer, Pharmaceutical Services, PharmaNet and Evaluation: personal communication, 2007 Mar 19)

APPENDIX 1D: UTILIZATION DATA FOR SOME ANTIHYPERTENSIVE DRUG CLASSES FROM PROVINCIAL DRUG PROGRAMS IN SASKATCHEWAN³

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	Mean
TZD	No. of persons (%)	24,063 (21.3)	25,983 (20.4)	26,971 (23.8)	26,663 (19.8)	27,126 (18.6)	26,161 (20.7)
	No. of prescriptions (%)	133,081 (19.0)	146,145 (18.3)	157,844 (17.6)	139,176 (14.6)	133,883 (12.7)	142,026 (16.1)
	Unit cost	--	--	--	--	--	--
	Expenditure (%)	\$773,682 (4.9)	\$849,599 (4.6)	\$978,060 (4.6)	\$995,759 (4.2)	\$982,324 (3.7)	\$915,885 (4.3)
	Expenditure/person	\$32	\$33	\$36	\$37	\$36	\$35
α-blockers	No. of persons (%)	2,181 (1.9)	2,016 (1.6)	1,839 (1.6)	1,534 (1.1)	1,426 (1.0)	1,799 (1.4)
	No. of prescriptions (%)	13,308 (1.9)	12,247 (1.5)	11,739 (1.3)	11,152 (1.2)	10,591 (1.0)	11,950 (1.4)
	Unit cost	--	--	--	--	--	--
	Expenditure (%)	\$241,779 (1.5)	\$227,246 (1.2)	\$207,726 (1.0)	\$194,637 (0.8)	\$181,553 (0.7)	\$210,588 (1.0)

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	Mean
	Expenditure/person	\$111	\$113	\$113	\$127	\$127	\$118
β-blockers	No. of persons (%)	18,241 (16.2)	20,929 (16.4)	22,709 (20.1)	23,198 (17.3)	26,232 (18.0)	22,262 (17.6)
	No. of prescriptions (%)	112,744 (16.1)	131,574 (16.4)	150,450 (16.8)	169,881 (17.9)	197,608 (18.8)	152,451 (17.3)
	Unit cost	--	--	--	--	--	--
	Expenditure (%)	\$1,234,617 (7.8)	\$1,362,292 (7.4)	\$1,853,884 (8.7)	\$2,311,842 (9.7)	\$2,375,896 (8.9)	\$1,827,706 (8.6)
	Expenditure/person	\$68	\$65	\$82	\$100	\$91	\$81
β-blockers + TZD	No. of persons (%)	1,164 (1.0)	1,208 (1.0)	1,153 (1.0)	1,100 (0.8)	1,103 (0.8)	1,146 (0.9)
	No. of prescriptions (%)	7,715 (1.1)	7,857 (1.0)	7,869 (0.9)	8,124 (0.9)	8,587 (0.8)	8,030 (0.9)
	Unit cost	--	--	--	--	--	--
	Expenditure (%)	\$174,219 (1.1)	\$178,207 (1.0)	\$179,743 (0.9)	\$186,554 (0.8)	\$186,055 (0.7)	\$180,956 (0.9)
	Expenditure/person	\$150	\$148	\$156	\$170	\$169	\$158
ACEI	No. of persons (%)	30,624 (27.1)	34,152 (26.8)	35,306 (31.2)	33,275 (24.8)	35,417 (24.3)	33,755 (26.7)
	No. of prescriptions (%)	196,949 (28.1)	220,656 (27.6)	240,876 (26.8)	253,423 (26.7)	277,429 (26.4)	237,867 (27.0)
	Unit cost	--	--	--	--	--	--
	Expenditure (%)	\$5,644,822 (35.7)	\$6,386,471 (34.9)	\$7,042,855 (33.17)	\$7,606,005 (31.8)	\$8,145,905 (30.6)	\$6,965,212 (32.9)
	Expenditure/person	\$184	\$187	\$199	\$229	\$230	\$206
ACEI + TZD	No. of persons (%)	3,605 (3.2)	4,150 (3.3)	4,427 (3.9)	4,544 (3.4)	4,991 (3.4)	4,343 (3.4)
	No. of prescriptions (%)	21,847 (3.1)	26,527 (3.3)	29,745 (3.3)	33,165 (3.5)	37,648 (3.6)	29,786 (3.4)
	Unit cost ¹	--	--	--	--	--	--
	Expenditure ² (%)	\$587,785 (3.7)	\$729,998 (4.0)	\$827,590 (3.9)	\$933,897 (3.9)	\$1,016,390 (3.8)	\$819,132 (3.9)
	Expenditure/person	\$163	\$176	\$187	\$206	\$204	\$187
ARB	No. of persons (%)	7,008 (6.2)	9,499 (7.5)	11,397 (10.1)	11,562 (8.6)	13,212 (9.1)	10,536 (8.3)
	No. of prescriptions (%)	41,458 (5.9)	57,131 (7.1)	72,749 (8.1)	83,910 (8.8)	99,564 (9.5)	70,962 (8.1)
	Unit cost	--	--	--	--	--	--
	Expenditure (%)	\$1,339,178	\$1,853,638	\$2,359,057	\$2,762,146	\$3,332,687 (12.5)	\$2,329,341 (11.0)

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	Mean
		(8.5)	(10.1)	(11.1)	(11.6)		
	Expenditure/person	\$191	\$195	\$207	\$239	\$252	\$217
ARB + TZD	No. of persons (%)	1,911 (1.7)	3,382 (2.7)	5,293 (4.7)	6,680 (5.0)	8,549 (5.9)	5,163 (4.1)
	No. of prescriptions (%)	10,334 (1.5)	19,159 (2.4)	32,810 (3.7)	46,782 (4.9)	63,157 (6.0)	34,448 (3.9)
	Unit cost	--	--	--	--	--	--
	Expenditure (%)	\$328,936 (2.1)	\$585,720 (3.2)	\$994,997 (4.7)	\$1,448,768 (6.1)	\$1,979,095 (7.4)	\$1,067,503 (5.0)
	Expenditure/person	\$172	\$173	\$188	\$217	\$232	\$196
CCB	No. of persons (%)	24,039 (21.3)	26,058 (20.5)	26,898 (23.7)	25,843 (19.2)	27,454 (18.9)	26,058 (20.6)
	No. of prescriptions (%)	164,272 (23.4)	178,981 (22.4)	193,374 (21.6)	204,926 (21.6)	223,760 (21.3)	193,063 (21.9)
	Unit cost	--	--	--	--	--	--
	Expenditure (%)	\$5,479,599 (34.7)	\$6,144,969 (33.6)	\$6,789,096 (32.0)	\$7,473,312 (31.3)	\$8,462,641 (31.7)	\$6,869,923 (32.4)
	Expenditure/person	\$228	\$236	\$252	\$289	\$308	\$263
Total	No. of persons (%)	112,836 (100)	127,377 (100)	113,284 (100)	134,399 (100)	145,510 (100)	126,681 (100)
	No. of prescriptions (%)	701,708 (100)	800,277 (100)	897,456 (100)	950,539 (100)	1,052,227 (100)	880,441 (100)
	Expenditure (%)	\$15,804,617 (100)	\$18,318,141 (100)	\$21,233,008 (100)	\$23,912,920 (100)	\$26,662,545 (100)	\$21,186,246 (100)

TZD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers

1, indicates average unit cost

2, indicates drug cost plus markup cost plus dispensing fee minus beneficiary contribution

3, data in 2005-06 is not complete

Data obtained from Canadian Institute for Health Information (Ruzica Subotic-Howell, CIHI: personal communication, 2007 Apr 4)

APPENDIX 1E: UTILIZATION DATA FOR SOME ANTIHYPERTENSIVE DRUG CLASSES FROM PROVINCIAL DRUG PROGRAMS IN MANITOBA

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
TZD	No. of persons (%)	17,851 (17.8)	21,207 (17.8)	22,651 (17.4)	25,305 (17.7)	24,713 (17.0)	24,701 (16.5)	22,738 (17.3)
	No. of prescriptions (%)	64,917 (14.1)	79,616 (14.0)	89,258 (13.8)	101,622 (14.2)	104,504 (13.9)	112,035 (13.7)	91,992 (13.9)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$606,983 (3.1)	\$784,141 (3.2)	\$946,033 (3.4)	\$1,147,151 (3.7)	\$1,200,931 (3.7)	\$1,282,437 (3.7)	\$994,613 (3.5)
	Expenditure/person	\$34	\$37	\$42	\$45	\$49	\$52	\$43
α-blockers	No. of persons (%)	2,486 (2.5)	2,496 (2.1)	2,376 (1.8)	2,223 (1.6)	1,994 (1.4)	1,843 (1.2)	2,236 (1.7)
	No. of prescriptions (%)	11,284 (2.4)	11,888 (2.1)	11,707 (1.8)	11,169 (1.6)	10,023 (1.3)	10,088 (1.2)	11,027 (1.7)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$406,332 (2.1)	\$420,403 (1.7)	\$417,938 (1.5)	\$404,723 (1.3)	\$368,606 (1.1)	\$357,050 (1.0)	\$395,842 (1.4)
	Expenditure/person	\$163	\$168	\$176	\$182	\$185	\$194	\$178
β-blockers	No. of persons (%)	18,581 (18.5)	22,481 (18.9)	25,165 (19.3)	28,264 (19.7)	29,272 (20.2)	30,790 (20.5)	25,759 (19.6)
	No. of prescriptions (%)	83,446 (18.1)	105,322 (18.6)	124,249 (19.2)	142,544 (19.9)	153,639 (20.5)	172,507 (21.2)	130,285 (19.7)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$1,970,125 (10.1)	\$2,501,095 (10.4)	\$2,965,580 (10.7)	\$3,464,726 (11.0)	\$3,519,979 (10.9)	\$3,768,503 (11.0)	\$3,031,668 (10.7)
	Expenditure/person	\$106	\$111	\$118	\$123	\$120	\$122	\$117
β-blockers + TZD	No. of persons (%)	335 (0.3)	387 (0.3)	408 (0.3)	429 (0.3)	403 (0.3)	397 (0.3)	393 (0.3)
	No. of prescriptions (%)	1,373 (0.3)	1,662 (0.3)	1,787 (0.3)	1,888 (0.3)	1,874 (0.3)	1,824 (0.2)	1,735 (0.3)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$55,892 (0.3)	\$72,192 (0.3)	\$78,299 (0.3)	\$83,277 (0.3)	\$75,175 (0.2)	\$60,080 (0.2)	\$70,819 (0.3)
	Expenditure/person	\$167	\$187	\$192	\$194	\$187	\$151	\$180
ACEI	No. of persons (%)	28,767 (28.7)	33,008 (27.7)	34,896 (26.8)	36,526 (25.5)	36,106 (24.9)	36,468 (24.3)	34,295 (26.1)

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
	No. of prescriptions (%)	145,344 (31.5)	173,167 (30.5)	190,240 (29.4)	201,255 (28.1)	203,591 (27.2)	219,379 (26.8)	188,829 (28.6)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$7,524,403 (38.4)	\$8,911,302 (36.9)	\$9,822,364 (35.4)	\$10,516,330 (33.5)	\$10,169,759 (31.5)	\$10,397,632 (30.3)	\$9,556,965 (33.8)
	Expenditure/person	\$262	\$270	\$281	\$288	\$282	\$285	\$278
ACEI + TZD	No. of persons (%)	1,793 (1.8)	2,307 (1.9)	2,620 (2.0)	3,033 (2.1)	3,122 (2.2)	3,278 (2.2)	2,692 (2.1)
	No. of prescriptions (%)	7,611 (1.7)	10,369 (1.8)	11,976 (1.9)	13,906 (1.9)	14,636 (2.0)	15,558 (1.9)	12,343 (1.9)
	Unit cost ¹	--	--	--	--	--	--	--
	Expenditure ² (%)	\$385,825 (2.0)	\$528,035 (2.2)	\$617,502 (2.2)	\$726,335 (2.3)	\$714,937 (2.2)	\$750,100 (2.2)	\$620,456 (2.2)
	Expenditure/person	\$215	\$229	\$236	\$239	\$229	\$229	\$230
ARB	No. of persons (%)	6,080 (6.1)	8,308 (7.0)	10,144 (7.8)	11,659 (8.1)	12,263 (8.4)	13,134 (8.8)	10,265 (7.8)
	No. of prescriptions (%)	27,794 (6.0)	39,066 (6.9)	49,532 (7.7)	57,012 (8.0)	62,505 (8.3)	68,532 (8.4)	50,740 (7.7)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$1,584,783 (8.1)	\$2,236,092 (9.3)	\$2,831,587 (10.2)	\$3,304,797 (10.5)	\$3,647,170 (11.3)	\$4,035,941 (11.8)	\$2,940,062 (10.4)
	Expenditure/person	\$261	\$269	\$279	\$283	\$297	\$307	\$283
ARB + TZD	No. of persons (%)	1,226 (1.2)	2,313 (1.9)	3,879 (3.0)	5,649 (3.9)	6,606 (4.6)	7,553 (5.0)	4,538 (3.5)
	No. of prescriptions (%)	4,781 (1.0)	9,435 (1.7)	16,353 (2.5)	24,286 (3.4)	29,674 (4.0)	34,414 (4.2)	19,824 (3.0)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$295,924 (1.5)	\$558,287 (2.3)	\$962,333 (3.5)	\$1,448,405 (4.6)	\$1,803,110 (5.6)	\$2,130,337 (6.2)	\$1,199,733 (4.2)
	Expenditure/person	\$241	\$241	\$248	\$256	\$273	\$282	\$257
CCB	No. of persons (%)	23,092 (23.0)	26,479 (22.3)	28,160 (21.6)	30,216 (21.1)	30,697 (21.1)	31,763 (21.2)	28,401 (21.6)
	No. of prescriptions (%)	114,154 (24.8)	136,433 (24.1)	151,417 (23.4)	163,300 (22.8)	168,984 (22.5)	184,438 (22.5)	153,121 (23.2)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$6,769,150	\$8,142,424	\$9,133,418	\$10,271,256	\$10,832,314	\$11,544,365	\$9,448,821

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
		(34.5)	(33.7)	(32.9)	(32.7)	(33.5)	(33.6)	(33.4)
	Expenditure/person	\$293	\$308	\$324	\$340	\$353	\$363	\$330
Total	No. of persons (%)	100,211 (100)	118,986 (100)	130,299 (100)	143,304 (100)	145,176 (100)	149,927 (100)	131,317 (100)
	No. of prescriptions (%)	460,704 (100)	566,958 (100)	646,519 (100)	716,982 (100)	749,430 (100)	818,775 (100)	659,895 (100)
	Expenditure (%)	\$19,599,417 (100)	\$24,153,972 (100)	\$27,775,055 (100)	\$31,367,000 (100)	\$32,331,980 (100)	\$34,326,446 (100)	\$28,258,978 (100)

TZD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers

1, indicates average unit cost

2, indicates drug cost plus markup cost plus dispensing fee minus beneficiary contribution

Data obtained from Canadian Institute for Health Information (Ruzica Subotic-Howell, CIHI: personal communication, 2007 Apr 4)

APPENDIX 1F: UTILIZATION DATA FOR SOME ANTIHYPERTENSIVE DRUG CLASSES FROM PROVINCIAL DRUG PROGRAMS IN NOVA SCOTIA

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
TZD	No. of persons (%)	25,671 (19.2)	26,441 (18.7)	27,138 (18.1)	28,785 (18.3)	28,997 (17.7)	29,138 (17.6)	27,695 (18.2)
	No. of prescriptions (%)	114,968 (17.4)	118,949 (16.9)	123,185 (16.3)	132,729 (16.6)	135,111 (16.5)	136,285 (16.3)	126,871 (16.6)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$1,022,681 (4.2)	\$1,082,991 (4.0)	\$1,202,002 (4.1)	\$1,276,813 (4.0)	\$1,335,949 (3.9)	\$1,371,091 (3.8)	\$1,215,255 (4.0)
	Expenditure/person	\$40	\$41	\$44	\$44	\$46	\$47	\$44
α-blockers	No. of persons (%)	3,369 (2.5)	3,969 (2.8)	3,974 (2.7)	4,344 (2.8)	4,493 (2.7)	4,957 (3.0)	4,184 (2.8)
	No. of prescriptions (%)	15,246 (2.3)	17,894 (2.5)	18,707 (2.5)	20,182 (2.5)	20,738 (2.5)	22,378 (2.7)	19,191 (2.5)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$454,840 (1.9)	\$566,961 (2.1)	\$602,238 (2.0)	\$644,809 (2.0)	\$687,037 (2.0)	\$753,198 (2.1)	\$618,181 (2.0)
	Expenditure/person	\$135	\$143	\$152	\$148	\$153	\$152	\$147
β-blockers	No. of persons (%)	31,597 (23.7)	33,117 (23.4)	35,477 (23.7)	38,443 (24.4)	39,098 (23.8)	40,078 (24.2)	36,302 (23.9)
	No. of prescriptions (%)	171,527 (25.9)	178,614 (25.3)	191,061 (25.2)	202,489 (25.3)	207,867 (25.3)	211,884 (25.3)	193,907 (25.4)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$3,779,171 (15.4)	4,027,833 (15.0)	\$4,358,541 (14.8)	\$4,562,862 (14.2)	\$4,719,272 (13.8)	\$4,951,383 (13.6)	\$4,399,844 (14.4)
	Expenditure/person	\$120	\$122	\$123	\$119	\$121	\$124	\$122
β-blockers + TZD	No. of persons (%)	--	--	--	--	--	--	--
	No. of prescriptions (%)	--	--	--	--	--	--	--
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	--	--	--	--	--	--	--
	Expenditure/person	--	--	--	--	--	--	--
ACEI	No. of persons (%)	36,996 (27.7)	39,305 (27.8)	40,368 (27.0)	40,471 (25.7)	41,341 (25.2)	41,358	39,973

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
							(24.9)	(26.3)
	No. of prescriptions (%)	178,379 (26.9)	191,742 (27.2)	204,071 (27.0)	208,997 (26.2)	211,931 (25.8)	213,491 (25.5)	201,435 (26.4)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$8,832,530 (36.1)	\$9,652,914 (36.0)	\$10,382,272 (35.2)	\$11,033,984 (34.4)	\$11,474,074 (33.5)	\$11,793,666 (32.4)	\$10,528,240 (34.4)
	Expenditure/person	\$239	\$246	\$257	\$273	\$278	\$285	\$263
ACEI + TZD	No. of persons (%)	93 (0.1)	170 (0.1)	227 (0.2)	290 (0.2)	344	361 (0.2)	248 (0.2)
	No. of prescriptions (%)	362 (0.1)	790 (0.1)	1,168 (0.2)	1,476 (0.2)	1,667 (1.0)	1,899 (0.2)	1,227 (0.2)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$12,984 (0.1)	\$33,328 (0.1)	\$50,656 (0.2)	\$69,134 (0.2)	\$81,210 (0.2)	\$93,935 (0.3)	\$56,875 (0.2)
	Expenditure/person	\$140	\$196	\$223	\$238	\$236	\$260	\$216
ARB	No. of persons (%)	7,184 (5.4)	9,447 (6.7)	12,596 (8.4)	14,538 (9.2)	17,941 (10.9)	18,260 (11.0)	13,328 (8.8)
	No. of prescriptions (%)	34,014 (5.1)	44,279 (6.3)	59,184 (7.8)	70,665 (8.8)	79,375 (9.7)	87,516 (10.5)	62,506 (8.2)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$1,820,770 (7.8)	\$2,400,952 (9.0)	\$3,247,916 (11.0)	\$4,028,424 (12.6)	\$4,768,758 (13.9)	\$5,551,939 (15.3)	\$3,636,460 (11.9)
	Expenditure/person	\$253	\$254	\$258	\$277	\$266	\$304	\$269
ARB + TZD	No. of persons (%)	--	--	--	--	--	--	--
	No. of prescriptions (%)	--	--	--	--	--	--	--
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	--	--	--	--	--	--	--
	Expenditure/person	--	--	--	--	--	--	--
CCB	No. of persons (%)	28,500 (21.4)	29,005 (20.5)	29,952 (20.0)	30,494 (19.4)	31,948 (19.5)	32,003 (19.3)	30,317 (19.9)
	No. of prescriptions (%)	148,033 (22.3)	152,521 (21.6)	159,421 (21.1)	162,603 (20.3)	163,785 (20.0)	165,138 (19.7)	158,584 (20.8)
	Unit cost	--	--	--	--	--	--	--
	Expenditure (%)	\$8,571,077	\$9,017,858	\$9,613,267	\$10,425,237	\$11,201,819	\$11,944,096	\$10,128,892

Product	Category	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	Mean
		(35.0)	(33.7)	(32.6)	(32.5)	(32.7)	(32.8)	(33.1)
	Expenditure/person	\$301	\$311	\$321	\$342	\$351	\$373	\$333
Total	No. of persons (%)	133,410 (100)	141,454 (100)	149,732 (100)	157,365 (100)	164,162 (100)	165,794 (100)	151,986 (100)
	No. of prescriptions (%)	662,529 (100)	704,789 (100)	756,797(100)	799,141 (100)	820,474 (100)	836,692 (100)	763,404 (100)
	Expenditure (%)	\$24,494,054 (100)	\$26,782,837 (100)	\$29,456,892 (100)	\$32,041,262 (100)	\$34,268,120 (100)	\$36,365,373 (100)	\$30,568,090 (100)

TZD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers

¹, indicates average unit cost

², indicates drug cost plus markup cost plus dispensing fee minus beneficiary contribution

Data obtained from Nova Scotia Ministry of Health (Judy McPhee, Manager, Drug Programs, Nova Scotia Department of Health: personal communication, 2007 April 13).

APPENDIX 2: CURRENT FORMULARY DATA FOR CANADIAN JURISDICTIONS

ATC Level 5	ATC Description	Metrics	Count of DINs/PDINs per Jurisdiction and Benefit Status																	
		Jurisdiction	AB		BC		FNIHB		MB	NB			NL		NS		ON		SK	
		Benefit Status	B	R	B	R	B	R	B	B	L	R	B	R	B	R	B	L	B	R
Thiazide diuretics																				
C03AA03	Hydrochlorothiazide		5	0	22	0	16	0	10	9	0	0	8	0	5	0	4	0	13	0
C03BA04	Chlorthalidone		1	0	11	0	2	0	5	2	0	0	2	0	2	0	3	0	2	0
C03BA08	Metolazone		1	0	6	0	1	0	3	2	0	0	1	0	1	0	2	0	2	0
C03BA11	Indapamide		13	0	0	11	18	0	14	6	0	0	11	0	0	0	11	0	13	0
C03EA01	Hydrochlorothiazide + Amiloride		5	0	6	0	7	0	6	5	0	0	5	0	5	0	4	0	5	0
C03EA01	Hydrochlorothiazide + Spironolactone		4	0	4	0	4	0	4	4	0	0	4	0	4	0	4	0	4	0
C03EA01	Hydrochlorothiazide +Triamterene		3	0	5	0	6	0	5	3	0	0	4	0	3	0	3	0	3	0
Alpha-blockers																				
C02CA01	Prazosin		12	0	20	0	15	0	18	10	0	0	12	0	9	0	12	0	10	0
C02CA04	Doxazosin		18	0	18	0	21	0	18	15	15	0	18	0	15	0	18	0	16	0
G04CA03	Terazosin		24	0	24	0	33	0	25	24	24	0	25	0	24	0	25	0	29	0
Beta-blockers																				
C07AA03	Pindolol		20	0	26	0	24	0	23	21	0	0	18	0	21	0	21	0	21	0
C07AA05	Propranolol		18	0	49	0	29	0	30	10	0	0	21	0	15	0	13	0	22	0
C07AA06	Timolol		8	0	13	0	11	0	12	8	0	0	8	0	8	0	9	0	9	0
C07AA12	Nadolol		10	0	11	0	13	0	9	10	0	0	11	0	9	0	11	0	11	0
C07AB02	Metoprolol		32	0	34	0	41	0	34	24	0	0	28	0	25	0	26	0	32	0
C07AB03	Atenolol		23	0	30	0	39	0	26	24	0	0	21	0	20	0	20	0	25	0
C07AB04	Acebutolol		27	0	33	0	38	0	29	26	0	0	24	0	27	0	27	0	27	0
C07AB07	Bisoprolol		8	0	8	0	7	0	8	8	0	0	8	0	8	0	6	0	0	8
C07AG01	Labetalol		5	0	11	0	4	0	7	4	0	0	4	0	4	0	5	0	4	0
C07AG02	Carvedilol		24	0	28	28	0	28	24	0	24	24	0	28	0	24	0	24	0	28
Beta-blockers + diuretics																				
C07CA03	Pindolol and other diuretics		2	0	2	0	2	0	2	2	0	0	2	0	2	0	2	0	2	0
C07CB03	Atenolol and other diuretics		4	0	6	0	4	0	4	4	0	0	4	0	4	0	4	0	6	0
	ACEI																			
C09AA01	Captopril		33	0	39	0	52	0	42	24	0	0	28	1	26	0	33	0	34	0
C09AA02	Enalapril		4	0	4	0	4	0	8	4	0	0	4	0	4	0	4	0	5	0
C09AA03	Lisinopril		9	0	12	0	13	0	10	9	0	0	10	0	9	0	12	0	9	0
C09AA04	Perindopril		3	0	3	0	3	0	3	3	0	0	2	0	2	0	3	0	3	0
C09AA05	Ramipril		4	0	9	0	4	0	9	4	0	0	4	0	4	1	4	0	4	0
C09AA06	Quinapril		4	0	4	0	4	0	4	4	0	0	4	0	4	0	4	0	4	0

ATC Level 5	ATC Description	Metrics	Count of DINs/PDINs per Jurisdiction and Benefit Status																	
		Jurisdiction	AB		BC		FNIHB		MB	NB			NL		NS		ON		SK	
		Benefit Status	B	R	B	R	B	R	B	B	L	R	B	R	B	R	B	L	B	R
C09AA07	Benazepril		4	0	4	0	3	0	4	4	0	0	3	0	4	0	4	0	4	0
C09AA08	Cilazapril		6	0	9	0	6	0	12	6	0	0	12	0	12	0	12	0	6	0
C09AA09	Fosinopril		10	0	14	0	12	0	14	10	0	0	14	0	12	0	14	0	14	0
C09AA10	Trandolapril		4	0	4	0	4	0	4	3	0	0	4	0	3	0	3	0	4	0
ACEI + diuretics																				
C09BA02	Enalapril and diuretics		2	0	2	0	2	0	2	2	0	0	2	0	2	0	0	0	2	0
C09BA03	Lisinopril and diuretics		6	0	8	0	6	0	6	6	0	0	6	0	6	0	4	0	6	0
C09BA04	Perindopril and diuretics		1	0	0	0	1	0	2	1	0	0	1	0	1	0	0	0	1	0
C09BA06	Quinapril and diuretics		3	0	3	0	3	0	3	3	0	0	3	0	3	0	3	0	3	0
C09BA08	Cilazapril and diuretics		1	0	1	0	1	0	1	1	0	0	1	0	2	0	1	0	1	0
ARB																				
C09CA01	Losartan		3	0	0	3	3	0	3	3	0	0	0	3	3	0	3	0	3	0
C09CA02	Eprosartan		2	0	0	1	2	0	3	2	0	0	0	2	2	0	2	0	2	0
C09CA03	Valsartan		4	0	0	4	3	0	5	2	0	2	0	2	2	0	4	0	5	0
C09CA04	Irbesartan		3	0	0	3	3	0	3	3	0	0	0	3	3	0	3	0	3	0
C09CA06	Candesartan		2	0	0	2	2	0	3	2	0	0	0	2	2	0	3	0	3	0
C09CA07	Telmisartan		2	0	0	2	2	0	2	2	0	0	0	2	2	0	2	0	2	0
ARB + diuretics																				
C09DA01	Losartan and diuretics		2	0	0	2	2	0	2	2	0	0	0	2	2	0	2	0	2	0
C09DA02	Eprosartan and diuretics		1	0	0	1	1	0	1	1	0	0	0	1	1	0	1	0	1	0
C09DA03	Valsartan and diuretics		3	0	0	3	3	0	3	3	0	0	0	2	3	0	3	0	3	0
C09DA04	Irbesartan and diuretics		2	0	0	2	2	0	3	2	0	0	0	2	2	0	2	0	2	0
C09DA06	Candesartan and diuretics		1	0	0	1	1	0	1	1	0	0	0	1	1	0	1	0	1	0
C09DA07	Telmisartan and diuretics		1	0	0	1	1	0	1	1	0	0	0	1	1	0	1	0	1	0
CCB																				
C08CA01	Amlodipine		2	0	2	0	2	0	2	0	2	2	0	2	2	0	2	0	2	0
C08CA02	Felodipine		6	0	12	0	6	0	14	6	0	0	6	0	7	0	6	0	6	0
C08CA05	Nifedipine		12	0	15	0	16	0	27	14	0	0	15	0	8	0	13	0	13	0
C08DA01	Verapamil		21	0	29	0	31	0	26	15	0	0	23	0	18	0	16	0	24	0
C08DB01	Diltiazem		66	9	74	0	71	0	72	65	0	0	54	0	60	0	54	0	60	0

Source: National Prescription Drug Utilization Information System (NPDUIS), Canadian Institute for Health Information (CIHI), 2007

Note:

AB, Alberta (as of October 2006); BC, British Columbia (as of February 2007); FNIHB, First Nations and Inuit Health Branch (as of October 2006); MB, Manitoba (as of December 2006); NB, New Brunswick (as of November 2006); NL, Newfoundland and Labrador (as of February 2007); NS, Nova Scotia (as of January 2007); ON, Ontario (as of December 2006); SK, Saskatchewan (as of December 2006)

"B" (Benefit) denotes drugs that are regular benefits, where no patient-specific justification to receive reimbursement is required.

"L" (Limited) denotes drugs that are listed on the Plan/Program and are limited benefits through regular (automated) adjudication processes against a set of Plan/Program-specific criteria (coded by either the prescriber or the pharmacy/service provider).

"R" (Restricted) denotes drugs that are listed on the Plan/Program and are restricted benefits through a formal request for coverage to be completed by the prescriber for patient-specific review, against a Plan/Program-specific set of criteria.

DIN/PDIN, drug information number/pseudoDIN

APPENDIX 3: LITERATURE SEARCH STRATEGY FOR CLINICAL EFFICACY STUDIES

Guide to Search Syntax (Ovid®)

\$	Truncation symbol, single character. Retrieve plural and variant ending of search terms.
ADJ	Proximity operator. Words must be near each other in any order.
ab	Search in article abstract.
cb	Chemicals & Biochemicals.
exp	Explode the search term. Retrieve the search concept plus all narrower terms.
mi	Miscellaneous descriptor.
mp	Unqualified search.
pt	Document type
rn	CAS Registry Number.
sh	Descriptor i.e., subject heading (a controlled, thesaurus term).
ti	Search in titles.
tn	Brand name

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
Ovid Multifile Search MEDLINE® (1966-present) BIOSIS Previews® (1985-present) EMBASE® (1980-present)	Human Date: (up to 18 May 2007)	<i>Concept #1 (Thiazide Diuretics)</i> 3. Sodium Chloride Symporter Inhibitors.sh. <i>[MeSH heading for MEDLINE®]</i> OR Thiazide Diuretic Agent.sh. <i>[EMTREE terms for EMBASE®]</i> OR Thiazide Diuretic Agent\$.mi. OR Thiazide Diuretic\$.cb. OR Thiazide-Like Diuretic\$.cb. <i>[controlled terms for BIOSIS®]</i> OR ((diuretic\$ ADJ2 thiazide\$) OR (benzothiadiazine diuretic\$) OR (potassium depleting diuretic\$) OR (sodium chloride cotransporter inhibitor\$) OR (thiazide sensitive NaCl cotransporter inhibitor\$)).ti,ab. <i>[Textwords searched in title, abstract]</i>

		OR Althiazide.nm. [Name of Substance Word for MEDLINE®] OR Altizide.sh. [EMTREE terms for EMBASE®] OR Althiazide\$.cb. OR Althiazide.mi. OR Althiazide.rn. OR Altizide\$.cb. OR Altizide.rn. OR Altizide.mi. [controlled term for BIOSIS®] OR 5588-16-9.rn. [registry number] OR (Althiazide OR Altizide OR (P adj 1779) OR Altozida OR Altizida OR Altizidum OR (CB adj 8093) OR (EINECS adj 226-994-8)).ti,ab. [Textwords searched in title, abstract] OR Dehydrosanol.nm. [Name of Substance Word for MEDLINE®] OR Bemetizide.sh. [EMTREE terms for EMBASE®] OR Bemetizide\$.cb. OR Bemetizide.rn. OR Bemetizide.mi. [controlled terms for BIOSIS®] OR
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		(Dehydrosanol).tn. [Brand names for EMBASE®] OR 1824-52-8.rn. [registry number] OR (Bemetizid\$ OR Dehydrosanol OR Bemetecide OR (BRN adj 0631888) OR (DIU adj 60) OR Pertensosanol OR (SU adj 7078)).ti,ab. [Textwords searched in title, abstract] OR Bendroflumethiazide.sh. [MeSH heading for MEDLINE®] OR Bendroflumethiazide.sh. [EMTREE terms for EMBASE®] OR Bendroflumethiazide.mi. OR Bendroflumethiazide\$.cb. OR Bendroflumethiazide.rn. OR Bendrofluazide.mi. OR Bendrofluazide\$.cb. OR Bendrofluazide.rn. [controlled term for BIOSIS®] OR (Aprinox OR Benzide OR Bendrofluazide OR Benuron OR Berkozide OR Centyl OR Esberizid OR Naturine OR Naturetin OR Neonaclex OR Pluryl\$ OR Salural OR Salures OR Sinesalin OR Sodiuretic OR Urizid).tn. [Brand names for EMBASE®] OR 73-48-3.rn. [registry number] OR
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		(Bendroflumethiazid\$ OR Bendrofluazide OR Aprinox OR BHFT OR Benzide OR Benzide-M OR (BL adj H368) OR (BRN adj 0373316) OR (Be adj 724-A) OR Bendrofluazid\$ OR Bendroflumatiiazid\$ OR Bentrider OR Benuron OR Benzhydroflumethiazid\$ OR Benzylhydroflumethiazid\$ OR Benzylrodiuran OR Berkozide OR Bristuric OR Bristuron OR (EINECS adj 200-800-1) OR (FT adj 8) OR (FT adj 81) OR Flumesil OR (HSDB adj 3293) OR Intolex OR Livesan OR Neorontyl OR Niagiril OR Nikion OR Esberizid OR NeoNaClex OR NeoNaClex OR Urizid OR Naturetin OR Centyl OR Naturetin OR Naturine OR Pluryl OR Berkozide OR Orsile OR Pluryl\$ OR Piusuril OR Poliuron OR Relan beta OR Repicin OR Salural OR Salures OR Sinesalin OR Sodiuretic OR Thiazidico OR Urlea).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Benzothiazide.nm. <i>[Name of Substance Word for MEDLINE®]</i> OR Benzthiazide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Benzothiazide.rn. OR Benzothiazide.mi. OR Benzothiazide.cb. OR Benzthiazide.rn. OR Benzthiazide.mi. OR Benzthiazide\$.cb. <i>[controlled term for BIOSIS®]</i> OR (Aquapres OR Aquatag OR Dihydrex OR Exna OR Fovane OR Regulon OR Urese).tn. <i>[Brand names for EMBASE®]</i> OR 91-33-8.rn. <i>[registry number]</i>
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		OR (Benzothiazid\$ OR Benzthiazid\$ OR Aqua-Scrip OR Aquapres OR Aquasec OR Aquatag OR Benzotiazid\$ OR Benzthiazid\$ OR Benzylthiomethylchlorothiazide OR Dihydrex OR Diucen OR Diucene OR Dytide N OR (EINECS adj 202-061-0) OR Edemex OR Exna OR Exosalt OR Fouane OR Fovane OR Freeuril OR (HSDB adj 3296) OR Hy-drine OR Lemazide OR Marazide OR Naclex Robins OR (P adj 1393) OR (Pfizer adj 1393) OR Pro-aqua OR Proaqua OR Rid-ema OR S-Aqua OR Urazide OR Urese).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Butizide.nm. <i>[Name of Substance Word for MEDLINE®]</i> OR Butizide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Butizide\$.cb. OR Butizide.rn. OR Butizide.mi. OR Buthiazide.rn. OR Buthiazide.mi. <i>[controlled term for BIOSIS®]</i> OR (Eunephran OR Saltucin).tn. <i>[Brand names for EMBASE®]</i> OR 2043-38-1.rn. <i>[registry number]</i> OR (Butizid\$ OR Buthiazide OR Hydrochlorbuthiazide OR Isobutylhydrochlorothiazide OR (EINECS adj 218-048-8) OR Eunephran OR Eunepran OR Modenol OR (S adj
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		3500) OR Saltucin OR (SU adj 6187) OR Thiabulazid OR Thiabutazide OR Thiobulazid OR Tiabutazide).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Chlorothiazide.sh. <i>[MeSH heading for MEDLINE®]</i> OR Chlorothiazide.sh. OR Chlorothiazide Derivative.sh. <i>[EMTREE terms for EMBASE®]</i> OR Chlorothiazide.rn. OR Chlorothiazide.mi. OR Chlorothiazide\$.cb. <i>[controlled term for BIOSIS®]</i> OR (Chlorosal OR Chlorurit OR Chlotride OR Clotride OR Diuresal OR Diurigen OR Diuril OR Diurilix OR Diuriwas OR Flumen OR Saluric OR Thiazide OR Urinex OR Yadalan).tn. <i>[Brand names for EMBASE®]</i> OR 58-94-6.rn. <i>[registry number]</i> OR (Chlorothiazid\$ OR Chlorthizid\$ OR Alurene OR (CCRIS adj 5999) OR Chlorosal OR Chlorthiazid\$ OR Chlortiazid OR Chlorurit OR Chlorzide OR Chlotride OR Clorotiazid\$ OR Clotride OR Diachlor OR Diuresal OR Diurigen OR Diuril OR Diurilix OR Diurite OR Diuriwas\$ OR Diutrid OR (EINECS adj 200-404-9) OR Flumen OR (HSDB adj 3030) OR Minzil OR (NSC adj 25693) OR Neo-dema OR Pahtlisan OR SK-Chlorothiazide OR Salisan OR Salunil OR Saluretil OR Saluric OR Thiazide OR Urinex OR Warduzide OR Yadalan).ti,ab.
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		<i>[Textwords searched in title, abstract]</i> OR Chlorthalidone.sh. <i>[MeSH heading for MEDLINE®]</i> OR Chlortalidone.sh. <i>[EMTREE terms for EMBASE®]</i> OR Chlorthalidone\$.cb. OR Chlorthalidone.rn. OR Chlorthalidone.mi. <i>[controlled term for BIOSIS®]</i> OR (Aquadon OR Clortalidone OR Chlorthalidone OR Higroton OR Higrotona OR Hydroton OR Hygroton OR Igroton OR Oxodolin OR Saluretin OR Thalitone OR Zambesil).tn. <i>[Brand names for EMBASE®]</i> OR 77-36-1.rn. <i>[registry number]</i> OR (Anilid OR Aquadon OR Bioralin OR (BRN adj 0312295) OR Clortalil OR Clortalidon\$ OR Chlortalidon\$ OR Clortil OR Chlorthalidon\$ OR Chlorphthalidolone OR Chlorphthalidone OR Chlortalidone OR Chlortalidonum OR Diuprol OR Drenidra OR Edemdal OR Euretico OR (G adj 33182) OR Hidrona OR Higroton OR Higrotona OR (HSDB adj 3035) OR Hydro-Long OR Hydroton OR Hygroton OR Igolina OR Igroton OR Isoren OR Natriuran OR Neolidona OR Novo-Thalidone OR (NSC adj 69200) OR Oksodolin OR Oradil OR Oxodolin OR Oxodoline OR Phthalamudine OR Phthalamidine OR Renon OR Saluretin OR Servidone OR Thalitone OR Urofinil OR
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		Zambesil).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Clopamide.sh. <i>[MeSH heading for MEDLINE®]</i> OR Clopamide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Clopamide\$.cb. OR Clopamide.rn. OR Clopamide.mi. <i>[controlled term for BIOSIS®]</i> OR (Adurix OR Brinaldix OR Brinedine).tn. <i>[Brand names for EMBASE®]</i> OR 636-54-4.rn. <i>[registry number]</i> OR (Clopamid\$ OR Adurix OR Aquex OR Brinaldix OR Brinedine OR Chlosudimeprimylum OR Clopamine OR (DT adj 327) OR (EINECS 211-261-7)).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Clorexolone.nm. <i>[Name of Substance Word for MEDLINE®]</i> OR Clorexolone.sh. <i>[EMTREE terms for EMBASE®]</i> OR
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		Clorexolone.rn. OR Clorexolone.mi. <i>[controlled term for BIOSIS®]</i> OR (Flonatril OR Nefrolan).tn. <i>[Brand names for EMBASE®]</i> OR 2127-01-7.rn. <i>[registry number]</i> OR (Clorexolon\$ OR (12833 adj R.P.) OR (BRN adj 0493411) OR Chlorexolone OR Chloresolone OR (EINECS adj 218-342-6) OR Flonatril OR Klorex OR (M&B adj 8430) OR Nefrolan).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Cyclopenthiazide.sh. <i>[MeSH heading for MEDLINE®]</i> OR Cyclopenthiazide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Cyclopenthiazide\$.cb. OR Cyclopenthiazide.rn. OR Cyclopenthiazide.mi. <i>[controlled term for BIOSIS®]</i> OR (Cyclopenthiazide OR Benesal OR Navidex OR Navidrex OR Navidrix).tn. <i>[Brand names for EMBASE®]</i> OR
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		742-20-1.rn. [registry number] OR (Cyclopentiazid\$ OR Cyclomethiazid\$ OR Cyclic S-oxides OR Cyclopentanes OR (BRN adj 0630346) OR Benesal OR (Ciba adj 8341-Su) OR Ciclopentiazid\$ OR Cyclometiazid OR Cyclopentiazid\$ OR (EINECS adj 212-012-5) OR (NSC adj 107679) OR Navidreks OR Navidrex OR Navidrix OR (SU adj 8341) OR Prothiazide OR Salimed OR Salimid OR Salurilo-C OR Tsiklometiazid OR Ultra-Minzil OR Navidex).ti,ab. [Textwords searched in title, abstract] OR Cyclothiazide.nm. [Name of Substance Word for MEDLINE®] OR Cyclothiazide.sh. [EMTREE terms for EMBASE®] OR Cyclothiazide\$.cb. OR Cyclothiazide.rm. OR Cyclothiazide.mi. [controlled term for BIOSIS®] OR (Anhydron OR Doburil OR Valmiran).tn. [Brand names for EMBASE®] OR 2259-96-3.rn. [registry number] OR (Cyclothiazid\$ OR Anhydron OR Aquirel OR (BRN adj 0722843) OR Ciclotiazida OR Ciclotiazide OR Cyclothiazidum OR Doburil OR (EINECS adj 218-859-
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		7) OR Fluidil OR (HSDB adj 3310) OR (L adj 35483) OR (Lilly adj 35,483) OR (MDi adj 193) OR Renazide OR Valmiran).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Diapamide.mp. <i>[Unqualified search for MEDLINE®, BIOSIS®]</i> OR Tiamizide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Vectren.tn. <i>[Brand names for EMBASE®]</i> OR 3688-85-5.rn. <i>[registry number]</i> OR (Diapamide OR Tiamizid\$ OR Thiamizide OR (BRN adj 2138735) OR (CI adj 456) OR CI-456 OR CN-36337 OR (CN adj 36337) OR (D adj 1593) OR (NSC adj 178204) OR Vectren).ti,ab. <i>[Textwords searched for title, abstract]</i> OR Epitizide.mp. <i>[Unqualified search for MEDLINE®]</i> OR Epitizide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Epitizide\$.cb. OR Epitizide.mi. OR Epithiazide.rn. OR
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		Epithiazide.mi. [controlled term for BIOSIS®] OR 1764-85-8.rn. [registry number] OR (Epitizid\$ OR Epithiazide OR Flurese OR (NSC adj 108164) OR P2105 OR P-2105 OR Thiaver).ti,ab. [Textwords searched in title, abstract] OR Fenquizone.nm. [Name of Substance Word for MEDLINE®] OR Fenquizone.sh. [EMTREE terms for EMBASE®] OR Fenquizone\$.cb. OR Fenquizone.rn. OR Fenquizone.mi. [controlled term for BIOSIS®] OR Idrolone.tn. [Brand names for EMBASE®] OR 20287-37-0.rn. [registry number] OR (Fenquizon\$ OR (EINECS adj 243-689-5) OR Fenchizone OR Idrolone OR (MG adj 13054).ti,ab. [Textwords searched in title, abstract] OR
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		Mebutizide.mp. <i>[Unqualified search for MEDLINE®]</i> OR Mebutizide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Mebutizide.rn. OR Mebutizide.mi. <i>[controlled term for BIOSIS®]</i> OR Neoniagar.tn. <i>[Brand names for EMBASE®]</i> OR 3568-00-1.rn. <i>[registry number]</i> OR (Mebutizid\$ OR Mebutiazide OR (EINECS adj 222-660-0) OR Neoniagar) .ti,ab. <i>[Textwords searched in title, abstract]</i> OR Mefruside.sh. <i>[MeSH heading for MEDLINE®]</i> OR Mefruside.sh. <i>[EMTREE terms for EMBASE®]</i> OR Mefruside\$.cb. OR Mefruside.rn. OR Mefruside.mi. <i>[controlled term for BIOSIS®]</i>
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		OR (Mefruside OR Baycaron).tn. [Brand names for EMBASE®] OR 7195-27-9.rn. [registry number] OR (Mefrusid\$ OR (B adj 1500) OR (Bay adj 1500) OR Bay Caron OR Baycaron OR (EINECS adj 230-562-4) OR (FBA adj 1500) OR (FDA adj 1902) OR Mefrusal).ti,ab. [Textwords searched in title, abstract] OR Hydrochlorothiazide.sh. [MeSH heading for MEDLINE®] OR Hydrochlorothiazide.sh. [EMTREE terms for EMBASE®] OR Hydrochlorothiazide\$.cb. OR Hydrochlorothiazide.rn. OR Hydrochlorothiazide.mi. [controlled term for BIOSIS®] OR (Hydrochlorothiazide OR Acesistem OR Acuilix OR Acuretic OR Aldactizide OR Aldoril OR Aquarius OR Aquazide OR Bremil OR Briazide OR Carozide OR Cidrex OR Clorana OR Dehydratin OR Diaqua OR Dichlotride OR Diclotride OR Didral OR Dihydran OR Disalunil OR Dithiazide OR Diural OR Diuret OR Diurex OR Drenol OR Dyazide OR Esidrex OR Esidrix OR Fluvin OR HCTZZ OR Hidrosaluretil OR Hydrex OR Hydril OR Hydrodiuril OR Hydropar OR Hydrosaluric OR Hypothiazid OR Hypothiazide OR Inderide OR Ivaugan OR Mazide OR Medozide OR
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		Microzide OR Moduretic OR Nefrix OR Neoflumen OR Neominzil OR Oretic OR Raunova OR Ridaq OR Roxane OR Sectrazide OR Selozone OR Spironazide OR Thiuretic OR Unazid OR Urodiazin OR Urozone OR Vasoretic OR Vetidrex OR Zide).tn. <i>[Brand names for EMBASE®]</i> OR 58-93-5.m. <i>[registry number]</i> OR (Acesistem OR Acuilix OR Acuretic OR “Aldactazide 25/25” OR Aldazida OR “Aldectazide 50/50” OR Aldoril D30 OR Aldoril D50 OR Apo-Hydro OR Aquarills OR Aquarius OR Aquazide H OR Aquazide-H OR (BRN adj 0625101) OR Bremil OR Briazide).ti,ab. OR ((CCRIS adj 2082) OR Carozide OR Catiazida OR Chlorizide OR Chlorosulthiadil OR Chlorsulfonamidodihydrobenzothiadiazine dioxide OR Chlorzide OR Chlothia OR Cidrex OR Clorana OR Concor Plus OR Condiuren).ti,ab. OR ((Dehydratin OR Diaqua OR Dichlorosal OR Dichlotiazid OR Dichlotride OR Diclotride OR Didral OR Didralin OR Di-etride OR Dihydran OR Dihydrochlorothiazid OR Dihydrochlorothiazide OR Dihydrochlorothiazidum OR Dihydrodiuril OR Direma OR Disalunil OR Disaluril OR Disothiazid OR Disothiazide OR Dithiazide OR (Diu adj 25 adj Vigt) OR Diu-melusin OR Diumelusin OR Diu melusin OR Diunorm OR Diural OR Diuret OR Diuretil OR Diurex OR Diurezin OR Diurepina OR Diurogen OR Dixidasi OR Drenol OR Dyazide)).ti,ab. OR ((EINECS adj 200-403-3) OR Esidrex OR Esidrix OR Esoidrina OR Fluvin OR HCTZ\$ OR HCTZ-Isis OR
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		HCTZZ OR HCZ OR Hexazide OR (HSDB adj 3096) OR Hidril OR Hidro-Niagrin OR Hydroclorozil OR Hydroclorothiazid\$ OR Hydroclorotiazida OR Hydrochlortiazid\$ OR Hidrofall OR Hidronol OR Hidrosaluretil OR Hidrotiazida OR Hudorex OR Hyclosid OR Hydrex OR Hydril OR Hydro Par).ti,ab. <i>OR</i> (Hydro-Aquil OR Hydroaquil OR Hydro-D OR Hydro-Diuril OR Hydro-Saluric OR Hydro-T OR (Hydro adj T) OR (Hydro adj Tonuron) OR (Hydro adj Z adj 50) OR Hydro Chlorothiazide OR Hydro Par OR Hydrochlorothiazid\$ OR Hydrochlorthiazid\$ OR Hydrocot OR Hydrodiuretic OR Hydrodiuril OR HydroDIURIL OR Hydrosaluric OR Hydro Saluric OR Hydrothide OR Hydrozide OR Hypothiazid OR Hypothiazide OR Hytrid).ti,ab. <i>OR</i> (Idroclorotiazide OR Idrotiazide OR “Inderide 80/25” OR Indroclor OR Ivaugan OR Jen-Diril OR Manuril OR Maschitt OR Mazide OR Medozide OR Megadiuril OR Microzide OR Mictrin OR Mikorten OR Modurcen OR Moduretic).ti,ab. <i>OR</i> (NCI-C55925 OR (NSC adj 53477) OR Natrinax OR Nefrix OR Nefrol OR Neo-Flumen OR Neo-Minzil OR Neo-codema OR Neo Codema OR Neoflumen OR Neo Flumen OR Neo Hydroclor OR Newtolide OR Niagar OR Novodiurex OR Novo-Hydrazide OR Oretic OR Pantemon OR Panurin OR PMS-Hydrochlorothiazide OR Raunova Plus OR Ridaq OR Ro-Hydrazide OR Roxane).ti,ab. <i>OR</i> ((SU adj 5879) OR Saldiuril OR Sectrazide OR Selopres OR Selozide OR Servithiazid OR Spironazide OR Tandiur OR Thiadril OR Thiaretic OR Thiuretic OR Unazid OR Urodiazin OR Urodiazine OR Urozide OR Vasoretic OR Vetidrex OR Zide).ti,ab. <i>[Textwords searched in title, abstract]</i>
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		OR Hydroflumethiazide.sh. [MeSH heading for MEDLINE®] OR Hydroflumethiazide.sh. [EMTREE terms for EMBASE®] OR Hydroflumethiazide\$.cb. OR Hydroflumethiazide.rn. OR Hydroflumethiazide.mi. [controlled term for BIOSIS®] OR (Bristurin OR Diucardin OR Diraudixin OR Hiserpin OR Leodrine OR Naclex OR Rontyl OR Saluron OR Vergonil).tn. [Brand names for EMBASE®] OR 135-09-01.rn. [registry number] OR (Hydroflumethiazid\$ OR Trifluoromethylhydrothiazide OR Diraudixin OR Diucardin OR (BRN adj 0342692) OR Bristab OR Bristurin OR Di-ademil OR Di-adenil OR Dihydroflumethiazide OR Diucardin OR Diuredemina OR Diurometon OR (EINECS adj 205-173-8) OR Elodrin OR Elodrine OR Enjit OR Finuret OR Flutizide OR Glomerulin OR (HSDB adj 3340) OR Hidroalogen OR Hidroflumetiazid\$ OR Hisperin OR Hydol OR Hydrenox OR Idroflumetiazide OR Leodrin OR Leodrine OR Metforylthiadiazin OR Metforylthiadiazine OR Metforylthiazidin OR (NSC adj 44627) OR NaClex OR Naciex OR Olmagran OR Rivosil OR Robezon OR Rodiuran OR Rontyl OR Saluron OR Sisuril OR Spandiuril oR Trifluoromethylhydrazide OR Vergonil).ti.ab.
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		<i>[Textwords searched in title, abstract]</i> OR Indapamide.sh. <i>[MeSH heading for MEDLINE®]</i> OR Indapamide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Indapamide\$.cb. OR Indapamide.rn. OR Indapamide.mi. OR Indapamide.mf. <i>[controlled term for BIOSIS®]</i> OR (Indapamide OR Lozide OR Arifon OR Clonix OR Dapa OR Dapamax OR Extur OR Fludex OR Indahexal OR Indalix OR Indamol OR Insig OR Ipamix OR Lorvas OR Lozol OR Millibar OR Natrilix OR Napamide OR Noranat OR Pressural OR Sicco OR Tandix OR Tertensif).tn. <i>[Brand names for EMBASE®]</i> OR 26807-65-8.rn. <i>[registry number]</i> OR (Indapamid\$ OR Metindamide OR (S adj 1520) OR (SE adj 1520)).ti,ab. OR (Agelan OR Apo-Indapamide OR Arifon OR Bajaten OR (BRN adj 1604026) OR Clonix OR Cormil OR Damide OR Dapa OR Dapamax OR Dapa-Tabs OR Daptril OR Diflerix OR Duremid OR (EINECS adj 248-012-7) OR Extur OR Fludamide OR Fludex oR Fluidema OR Frumeron OR Gen-Indapamide OR Hydro-Less OR
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		Inamide OR Indacar OR Indahexal OR Indaflex OR Indalix OR Indamol OR Indanorm OR (Indapamide adj 1.25) OR Indapress OR Indapuren OR Indolin OR Indopamide OR Insig OR Ipamix OR Lixamide OR Lorvas OR Lozide OR Lozol OR Magniton-R OR Millibar OR Natrilix OR Napamide OR Naplin OR Naride OR Nindaxa OR Noranat OR Nu-Indapamide OR PHL-Indapamide OR Pressurai OR Pressural OR (RHC adj 2555) OR Rinalix OR Riva-Indapamide OR Sicco OR Tandix OR Tertensif OR Transipen OR (USV adj 2555) OR Veroxil).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Methyclothiazide.sh. <i>[MeSH heading for MEDLINE®]</i> OR Methyclothiazide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Methyclothiazide\$.cb. OR Methyclothiazide.rn. OR Methyclothiazide.mi. <i>[controlled term for BIOSIS®]</i> OR (Aquatensen OR Diuretic OR Enduron OR Thiazidil).tn. <i>[Brand names for EMBASE®]</i> OR 135-07-9.rn. <i>[registry number]</i> OR (Methyclothiazid\$ OR Aquatensen OR (BRN adj 0765361) OR CI-625 OR (Ciba adj 7272-Su) OR Duretic OR (EINECS adj 205-172-2) OR Enduron OR Enduronum OR (HSDB adj 3363) OR Methiclothiazide OR Methylchlorothiazide OR Methycyclothiazid\$ OR
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		Meticlotiazid\$ OR (NSC adj 110431) OR NSC-110431 OR Naturon OR Thiazidil).ti,ab. <i>[Textwords searched in title, abstract]</i> OR (meticran\$ OR E-103-E).mp. <i>[unqualified search in all]</i> OR 1084-65-7.rn. <i>[registry number]</i> OR Metolazone.sh. <i>[MeSH heading for MEDLINE®]</i> OR Metolazone.sh. <i>[EMTREE terms for EMBASE®]</i> OR Metolazone\$.cb. OR Metolazone.rn. OR Metolazone.mi. <i>[controlled term for BIOSIS®]</i> OR (Diulo OR Metenix OR Miclox OR Microx OR Mykrox OR Zaroxolyn OR Zaroxolyne).tn. <i>[Brand names for EMBASE®]</i> OR 17560-51-9.rn. <i>[registry number]</i> OR (Metolazon\$ OR Birobin OR (BRN adj 0965505) OR Diondel OR Diulo OR (HSDB adj 3367) OR Metalazone OR Metalozone OR Metenix OR Miclox OR Micros OR Microx OR Mykrox OR Oldren OR Pavedal OR (SR adj
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		720 adj 22) OR Zaroxolyn OR Zaroxolyne).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Polythiazide.sh. <i>[MeSH heading for MEDLINE®]</i> OR Polythiazide.sh. <i>[EMTREE terms for EMBASE®]</i> OR Polythiazide\$.cb. OR Polythiazide.rn. OR Polythiazide.mi. <i>[controlled term for BIOSIS®]</i> OR (Drenusil OR Nephril OR Renese).tn. <i>[Brand names for EMBASE®]</i> OR 346-18-9.rn. <i>[registry number]</i> OR (Polythiazid\$ OR (BRN adj 0770371) OR (CCRIS adj 6094) OR Drenusil OR (EINECS adj 206-468-4) OR (HSDB adj 850) OR Nephril OR (NSC adj 108161) OR (P adj 2525) OR P-2525 OR Politiazid\$ OR Polythiaside OR Renese).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Quinethazone.nm. <i>[Name of Substance Word for MEDLINE®]</i> OR Quinethazone.sh.
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		<i>[EMTREE terms for EMBASE®]</i> OR Quinethazone\$.cb. OR Quinethazone.rm. OR Quinethazone.mi. <i>[controlled term for BIOSIS®]</i> OR (Aquamox OR Hydromox).tn. <i>[Brand names for EMBASE®]</i> OR 73-49-4.rm. <i>[registry number]</i> OR (Quinethazon\$ OR Aquamox OR (BRN adj 0818554) OR (CCRIS adj 6098) OR Chinetazone OR Chinethazon OR Chinethazone OR Chinethazonum OR (CL adj 36010) OR (EINECS adj 200-801-7) OR Guinethazone OR (HSDB adj 3392) OR Hydromox OR Idrokin OR Kinetazone OR Quietazon\$ OR Quinethazon).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Trichlormethiazide.sh. <i>[MeSH heading for MEDLINE®]</i> OR Tetrachlormethiazide.nm. <i>[Name of substance word for MEDLINE®]</i> OR (Trichlormethiazide OR Teclothiazide).sh. <i>[EMTREE terms for EMBASE®]</i> OR Trichlormethiazide\$.cb. OR Trichlormethiazide.rm. OR
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		Trichlormethiazide.mi. <i>[controlled term for BIOSIS®]</i> OR (Aquazide OR Diurese OR Esmarin OR Eurinol OR Fluitran OR Flutra OR Metahydrin OR Methahydrin OR Naqua OR Naquasone OR Salurin OR Triazide OR Triflumen).tn. <i>[Brand names for EMBASE®]</i> OR (133-67-5 OR 4267-05-4).rn. <i>[registry number]</i> OR (Trichlormethiazid\$ OR Achletin OR Anistadin OR Aponorin OR Aquazide OR (BRN adj 0629145) OR Carvacron OR Chlopolidine OR (Ciba adj 7057-Su) OR Cretonin OR Diu-Hydrin OR Diurazida OR Diurese OR Diuroral OR (EINECS adj 205-118-8) OR Esmarin OR Eurinol OR Fluitran OR Flurese OR Flutra OR Gangesol OR (HSDB adj 3406) OR Hydrotrichlorothiazide OR Intromene OR Esestran OR Kubacron OR Metahydrin OR Methahydrin OR Nacqua OR Naquasone OR (NSC adj 61560) OR Nakva OR Naqua OR Salurin OR Schebitran OR Tachionin OR Tolcasone OR Triazide OR Trichlordiuride OR Trichlormetazid\$ OR Trichlormethiadiazide OR Trichlormethiazide OR Trichloromethiazide OR Trichloromethylhydrochlorothiazide OR Triflumen OR tetrachlormethiazide OR tetrachloromethiazide OR teclothiazid\$).ti,ab. <i>[Textwords searched in title, abstract]</i> OR Tripamide.nm. <i>[Name of substance word for MEDLINE®]</i> OR Tripamide.sh. <i>[EMTREE terms for EMBASE®]</i>
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		OR Normonal.tn. [Trade name for EMBASE®] OR Tripamide.cb. [controlled terms for BIOSIS®] OR 73803-48-2.rn. [registry number] OR (tripamid\$ OR Normonal OR E 614 OR E614).ti,ab. [Textwords searched in title, abstract] OR Xipamide.sh. [MeSH heading for MEDLINE®] OR Xipamide.sh. [EMTREE terms for EMBASE®] OR Xipamide\$.cb. OR Xipamide.rn. OR Xipamide.mi. [controlled term for BIOSIS®] OR (Xipamide OR Salicylamide OR Aquaphor OR Aquaphoril OR Aquavor OR Diurex OR Diurexan OR Lumitens OR Zipix).tn. [Brand names for EMBASE®] OR 14293-44-8.rn.
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		<i>[registry number]</i> OR (Xipamid\$ OR Xylenes OR Salicylamides OR Acquaphoril OR Aquaforil OR Aquaphoril OR Aquaphor OR Aquavor OR (Be adj 1293) OR (BRN adj 2778357) OR Diurex OR Diurexan OR (EINECS adj 238-216-4) OR Lumitens OR (MJF adj 10,938) OR (MJF adj 10938) OR Xypamide OR Zipix).ti,ab. <i>[Textwords searched in title, abstract]</i> OR (Zidapamid\$ OR isodapamid\$ OR (EINECS adj 278-321-2)).mp. <i>[unqualified search in all]</i> OR 75820-08-5.rn. <i>[registry number]</i> AND <i>Concept #2 (Hypertension)</i> 3. exp Hypertension/ <i>[MeSH heading for MEDLINE®]</i> OR exp Hypertension/ <i>[EMTREE term for EMBASE®]</i> OR Hypertension\$.ds,mi. <i>[controlled term for BIOSIS®]</i> OR (hypertens\$ OR antihypertens\$ OR anti hypertens\$ OR blood pressure lower\$ OR ((elevated OR high OR increased) ADJ blood pressure)).ti,ab. <i>[Textwords searched in title, abstract]</i>
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		AND Concept #3 (Controlled Trial OR Sys. Review Filters) 3. exp Controlled Clinical Trials/ OR Clinical Trials.sh. (1980-1994) OR exp Epidemiologic Research Design/ OR Epidemiologic Methods.sh. (1970-1997) OR Research Design.sh. (1971-1997) OR Multicenter Studies.sh. <i>[MeSH headings for MEDLINE®]</i> (Multicenter Study OR Randomized Controlled Trial OR Controlled Clinical Trial).pt. <i>[MeSH headings for MEDLINE®]</i> (Major Clinical Study OR Multicenter Study OR Randomized Controlled Trial).sh. OR exp Controlled Study/ OR exp Evidence Based Medicine/ <i>[EMTREE terms for EMBASE®]</i> (Multicenter Study OR Randomized Controlled Trial OR Randomized Clinical Trial OR Randomized Trial OR Evidence-Based Medicine).mp. <i>[unqualified search for BIOSIS®]</i> (random\$ OR sham\$ OR placebo\$ OR (singl\$ ADJ (blind\$ OR dumm\$ OR mask\$)) OR (doubl\$ ADJ (blind\$ OR dumm\$ OR mask\$))).ti,ab. ((tripl\$ ADJ (blind\$ OR dumm\$ OR mask\$)) OR (trebl\$ ADJ (blind\$ OR dumm\$ OR mask\$))).ti,ab. ((control\$ ADJ (study OR studies OR trial\$)) OR rct\$).ti,ab. ((multicent\$ OR multi cent\$) ADJ (study OR studies OR trial\$)).ti,ab. <i>[Textwords searched in title, abstract]</i> Meta-Analysis.sh. OR Follow-Up Studies.sh. (1977- 1979) OR Outcome and Process Assessment.sh. (1977- 1979) OR Research.sh. (1980-1982) OR Research Design.sh. (1980-1988) OR Statistics.sh. (1980-1988) OR exp Technology Assessment, Biomedical/ OR Meta- Analysis.pt. <i>[MeSH headings for MEDLINE®]</i> Meta Analysis.sh. OR Systematic Review.sh. <i>[EMTREE term for EMBASE®]</i> (Meta Analysis OR Metaanalysis OR Systematic Review
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		OR Biomedical Technology Assessment).mp. <i>[unqualified search for BIOSIS®]</i> ((systematic\$ ADJ (literature review\$ OR review\$ OR overview\$)) OR (methodologic\$ ADJ (literature review\$ OR review\$ OR overview\$))).ti,ab. ((quantitative ADJ (review\$ OR overview\$ OR synthes\$)) OR (research ADJ (integration\$ OR overview\$))).ti,ab. ((integrative ADJ2 (review\$ OR overview\$)) OR (collaborative adj (review\$ OR overview\$)) OR pool\$ analy\$).ti,ab. (data synthes\$ OR data extraction\$ OR data abstraction\$).ti,ab. (handsearch\$ OR hand search\$).ti,ab. (mantel haenszel OR peto OR der simonian OR dersimonian OR fixed effect\$ OR latin square\$).ti,ab. (meta analy\$ OR metaanaly\$ OR met analy\$ OR metanaly\$ or health technology assessment\$ OR HTA OR HTAs OR biomedical technology assessment\$ OR bio-medical technology assessment\$).ti,ab. (meta regression\$ OR metaregression\$ OR mega regression\$).ti,ab. <i>[Textwords searched in title, abstract]</i>
DIALOG OneSearch® BIOSIS Previews® (1969-1984) EMBASE® (1974-1979)	Human	Same controlled terms and keywords as per Ovid search. Appropriate syntax used.
PubMed	Human Date: (up to 1 May 2007)	Same MeSH and keywords as per Ovid MEDLINE® search. Appropriate syntax used.
Cochrane Library (Issues 2, 3, 4, 2006; Issue 1, 2007)		Same MeSH and keywords as per Ovid MEDLINE® search, excluding study design filter. Appropriate syntax used.
Websites of health technology assessment (HTA) and related agencies; trial registries; other databases		AHRQ; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; LILACS etc.

Internet searching		Google™ search engine and others, as appropriate
Appropriate societies/association websites		For conference abstracts.

APPENDIX 4: DATA EXTRACTION FORM

Reviewer initial:

Study			
First author, year of publication			
Study Characteristics			
Objective			
Publication type			
Sponsor			
Countries			
No of centres			
Study type			
Washout period (wk)			
Study period (mth)			
Comparison arms			
Dosage			
Number of patients randomized (n)			
Number of patients completed trials (n)			
Number of withdrawals (n)			
Comment			
Patient baseline characteristics			
Inclusion			
Exclusion			
Age (y)			
Gender (male/female, %)			
Height (m)			
Weight (kg)			
BMI (kg/m ²)			
Heart rate (bpm)			
BP measurement Peak (P)? Trough (T)?			
Sitting systolic BP (mmHg)			
Sitting diastolic BP (mmHg)			
Supine systolic BP (mmHg)			

Supine diastolic BP (mmHg)			
Outcomes			
<i>Primary</i>			
Major cardiovascular events (n)			
Coronary heart disease (n)			
Congestive heart failure (n)			
Myocardial infarction (n)			
Myocardial ischemia			
Major vascular events (n)			
Stroke (n)			
Number of withdrawals due to adverse events (n)			
<i>Secondary</i>			
BP measurement Peak (P)? Trough (T)?			
Sitting systolic BP (mmHg)			
Sitting diastolic BP (mmHg)			
Supine systolic BP (mmHg)			
Supine diastolic BP (mmHg)			
Change of systolic BP (mmHg), p value			
Change of diastolic BP (mmHg), p value			
Augmentation index Baseline Endpoint			
Renal vascular resistance index Baseline Endpoint			
CV mortality (n)			
Total mortality (n)			
Quality of life			

BMI, body mass index; BP, blood pressure; bpm, beats per minute; CVD, cardiovascular disease

APPENDIX 5: TRIAL QUALITY ASSESSMENT FORM

No	Category	Score
1	Randomization: Was the study described as randomized (i.e., including words such as randomly, random, randomization)? A trial reporting that it is "randomized" is to receive one point. Yes=1 or No=0	
	Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point. Appropriate =1, not appropriate =0	
	If the report describes the trial as randomized and uses an inappropriate method of randomization (e.g., date of birth, hospital numbers), a point is deducted. Inappropriate = -1	
2	Double-blinding: Was the study described as double-blind? A trial reporting that it is "double-blind" is to receive one point. Yes =1, no =0.	
	Trials describing an appropriate method of double-blinding (identical placebo: colour, shape, taste) are to receive an additional point. Yes =1, No =0	
	If the report describes a trial as double-blind and uses an inappropriate method (e.g. comparison of tablets versus injection with no dummy), a point is deducted. Inappropriate = -1	
3	Withdrawals and dropouts: Was there a description of withdrawals and dropouts? A trial reporting the number and reasons for withdrawals or dropouts is to receive one point. If there is no description, no point is given. Yes =1, No= 0	
	Total score (for above 3 categories) on Jadad scale (0-2 = Low, 3- 5 = High)	
		Adequacy level*
4	Adequacy of allocation concealment: Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes etc. =Adequate Alternation; reference to case record # or date of birth, etc. = Inadequate Allocation concealment is not reported, or, fits neither category. = Unclear	
5.	Blinding of outcome assessors: Were the outcome assessors blind to the intervention (Yes, no, partially, or NR)?	
6.	Analyses Were the analyses by intent-to treat (ITT) (yes, no, partially or NR)?	

*Adequacy level = adequate, inadequate or unclear; NR = not reported

APPENDIX 6: INCLUDED TRIALS

No	Trial	Reference
Trials related to question 1		
1	ALLHAT ¹²	Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). <i>JAMA</i> 2002;288(23):2981-97.
2	ANBP-1 ¹³	The Australian therapeutic trial in mild hypertension. Report by the Management Committee. <i>Lancet</i> 1980;1(8181):1261-7.
3	ANBP-2 ¹⁴	Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. <i>N Engl J Med</i> 2003;348(7):583-92. Available: http://content.nejm.org/cgi/content/abstract/348/7/583 .
4	ANBPS ¹⁵	Treatment of mild hypertension in the elderly. A study initiated and administered by the National Heart Foundation of Australia. <i>Med J Aust</i> 1981;2(8):398-402.
5	Barracough et al ¹⁶	Control of moderately raised blood pressure. Report of a co-operative randomized controlled trial. <i>Br Med J</i> 1973;3(5877):434-6.
6	Carter AB ¹⁷	Carter AB. Hypotensive therapy in stroke survivors. <i>Lancet</i> 1970;1(7645):485-9.
7	EWPHE ¹⁸	Amery A, Birkenhäger W, Brixko P, Bulpitt C, Clement D, Deruyttere M, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. <i>Lancet</i> 1985;1(8442):1349-54.
8	HAPPHY ¹⁹	Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. <i>J Hypertens</i> 1987;5(5):561-72.
9	HSCSG ²⁰	Hypertension stroke cooperative study group. Effect of antihypertensive treatment on stroke recurrence. <i>JAMA</i> 1974;229(4):409-18
10	HYVET ²¹	Bulpitt CJ, Beckett NS, Cooke J, Dumitrascu DL, Gil-Extremera B, Nachev C, et al. Results of the pilot study for the Hypertension in the Very Elderly Trial. <i>J Hypertens</i> 2003;21(12):2409-17.
11	INSIGHT ²²	Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). <i>Lancet</i> 2000;356(9227):366-72.
12	MAPHY ^{23,113}	1. Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G. Primary prevention with metoprolol in patients with hypertension. Mortality results from the MAPHY study. <i>JAMA</i> 1988;259(13):1976-82. 2. Wikstrand J, Warnold I, Tuomilehto J, Olsson G, Barber HJ, Eliasson K, et al. Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY Study. <i>Hypertension</i> 1991;17(4):579-88
13	MIDAS ²⁴	Borhani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Terris M, Carr AA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. <i>JAMA</i> 1996;276(10):785-91.
14	MRC-mild ²⁵	Peart S, Broughton PMG, Dollery CT, Hudson MF, Lever AF, Meade TW, et al. Medical research council trial of treatment of mild hypertension principal results. <i>Br Med J</i> 1985;291(6488):97-104.

No	Trial	Reference
15	MRC-old ²⁶	Peart S, Brennan PJ, Broughton P, Dollery C, Hudson MF, Lever AF, et al. Medical Research Council trial of treatment of hypertension in older adults: Principal results. <i>Br Med J</i> 1992;304(6824):405-12
16	NICS-EH ²⁷	National Intervention Cooperative Study in Elderly Hypertensives Study Group. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. <i>Hypertension</i> 1999;34(5):1129-33. Available: http://hyper.ahajournals.org/cgi/content/full/34/5/1129 .
17	OSLO ²⁸	Helgeland A. Treatment of mild hypertension: a five year controlled drug trial. The Oslo study. <i>Am J Med</i> 1980;69(5):725-32
18	PATS ²⁹	Liu L, Gong L, Liu G, Wang J, Fang W, Liu GZ, et al. Post-stroke antihypertensive treatment study. A preliminary result. <i>Chin Med J (Engl)</i> 1995;108(9):710-7.
19	PHS ³⁰	Smith WM, US Public Health Service Hospitals Cooperative Study Group. Treatment of mild hypertension: results of a ten-year intervention trial. <i>Circ Res</i> 1977;40(5 Suppl 1):I-98-I-105.
20	SHELL ³¹	Malacco E, Mancina G, Rappelli A, Menotti A, Zuccaro MS, Coppini A, et al. Treatment of isolated systolic hypertension: the SHELL Study results. <i>Blood Press</i> 2003;12(3):160-7.
21	SHEP ³²	SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. <i>JAMA</i> 1991;265(24):3255-64
22	SHEP-PS ³³	Perry HM, Smith WM, McDonald RH, Black D, Cutler JA, Furberg CD, et al. Morbidity and mortality in the Systolic Hypertension in the Elderly Program (SHEP) pilot study. <i>Stroke</i> 1989;20(1):4-13.
23	VA-I ³⁴	Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. <i>JAMA</i> 1967;202(11):1028-34.
24	VA-II ³⁵	Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. <i>JAMA</i> 1970;213(7):1143-52.
25	VA-NHLBI ³⁶	Mitchell Perry H, Goldman AI, Lavin MA, Schanper HW, Fitz AE, Frohlich ED, et al. Evaluation of drug treatment in mild hypertension: VA-NHLBI feasibility trial. Plan and preliminary results of a two-year feasibility trial for a multicenter intervention study to evaluate the benefits versus the disadvantages of treating mild hypertension. Prepared for the Veterans Administration-National Heart, Lung, and Blood Institute Study Group for Evaluating Treatment in Mild Hypertension. <i>Ann N Y Acad Sci</i> 1978;304:267-92
26	VHAS ³⁷	Zanchetti A, Rosei EA, Dal Palù C, Leonetti G, Magnani B, Pessina A. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. <i>J Hypertens</i> 1998;16(11):1667-76.
Trials related to question 3		
1	AASK ^{59,68}	1. Wright JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. <i>JAMA</i> 2002;288(19):2421-31. 2. Contreras G, Greene T, Agodoa LY, Cheek D, Junco G, Dowie D, et al. Blood pressure control, drug therapy, and kidney disease.

No	Trial	Reference
		<i>Hypertension</i> 2005;46(1):44-50.
2	ABCD-H ⁶⁰	Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. <i>Diabetes Care</i> 2000;23(Suppl 2):B54-B64.
3	ABCD-N ⁶¹	Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. <i>Kidney Int</i> 2002;61(3):1086-97.
4	CSG ⁶²	Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ, Collaborative Study Group. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. <i>Am J Kidney Dis</i> 1999;34(5):809-17.
5	HOT ^{63,114}	1. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. <i>Lancet</i> 1998;351(9118):1755-62. 2. Ruilope LM, Salvetti A, Jamerson K, Hansson L, Warnold I, Wedel H, et al. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. <i>J Am Soc Nephrol</i> 2001;12(2):218-25
6	Ikeda et al ⁶⁴	Ikeda N, Suzuki H, Moriwaki K, Sugahara S, Kanno Y, Okada H, et al. Intensive blood pressure reduction is beneficial in patients with impaired cardiac function coexisting with chronic renal insufficiency. <i>Hypertens Res</i> 2002;25(1):41-8.
7	MDRD ^{65,115}	Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. <i>Ann Intern Med</i> 2005;142(5):342-51. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. <i>N Engl J Med</i> 1994;330(13):877-84.
8	REIN-2 ⁶⁶	Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. <i>Lancet</i> 2005;365(9463):939-46.
9	Toto et al ⁶⁷	Toto RD, Mitchell HC, Smith RD, Lee HC, McIntire D, Pettinger WA. "Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis. <i>Kidney Int</i> 1995;48(3):851-9.
Trials related to quality of life		
1	ALPINE ³⁹	Lindholm LH, Persson M, Alaupovic P, Carlberg B, Svensson A, Samuelsson O. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE Study). <i>J Hypertens</i> 2003;21(8):1563-74.
2	Bird et al ⁴⁰	Bird AS, Blizard RA, Mann AH. Treating hypertension in the older person: an evaluation of the association of blood pressure level and its reduction with cognitive performance. <i>J Hypertens</i> 1990;8(2):147-52
3	Boissel et al ⁴¹	Boissel JP, Collet JP, Lion L, L., Ducruet T, Moleur P, et al. A randomized comparison of the effect of four antihypertensive monotherapies on the subjective quality of life in previously untreated asymptomatic patients: field trial in general practice. <i>Journal of hypertension</i> 1995;13(9):1059-67

No	Trial	Reference
4	Chang et al ⁴²	Chang SW, Fine R, Siegel D, Chesney M, Black D, Hulley SB. The impact of diuretic therapy on reported sexual function. <i>Arch Intern Med</i> 1991;151(12):2402-8
5	EWPHE ⁴³	Fletcher A, Amery A, Birkenhäger W, Bulpitt C, Clement D, de Leeuw P, et al. Risks and benefits in the trial of the European Working Party on High Blood Pressure in the Elderly. <i>J Hypertens</i> 1991;9(3):225-30
6	Glick et al ⁴⁴	Glik DC, Steadman MS, Michels PJ, Mallin R. Antihypertensive regimen and quality of life in a disadvantaged population. <i>J Fam Pract</i> 1990;30(2):143-9
7	HAPPHY ¹⁹	Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. <i>J Hypertens</i> 1987;5(5):561-72
8	Lacourciere et al ⁴⁵	Lacourciere Y. Analysis of well-being and 24-hour blood pressure recording in a comparative study between indapamide and captopril. <i>Am J Med</i> 1988;84(Suppl 1B):47-52
9	Malmqvist et al ⁴⁶	Malmqvist K, Kahan T, Dahl M. Angiotensin II type 1 (AT1) receptor blockade in hypertensive women: benefits of candesartan cilexetil versus enalapril or hydrochlorothiazide. <i>Am J Hypertens</i> 2000;13(5 Pt 1):504-11
10	Martin et al ⁴⁷	Maldonado MA, Oliva VJA, Aznar CJ, Gil EB. Quality of life in hypertensive patients treated with captopril versus hydrochlorothiazide. A study of 1182 ambulatory patients. <i>Eur J Intern Med</i> 1994;5(4):293-8
11	Metelitsa et al ⁴⁸	Metelitsa VI, Douda SG, Ostrovskaya TP, Filatova NP, Muhamedganova GF, Vygodin VA, et al. Long-term monotherapy with antihypertensives and quality of life in patients with mild to moderate arterial hypertension: a multicentre study. <i>Journal of Drug Development & Clinical Practice</i> 1996;8(2):61-76
12	MRC-mild ^{40,49}	Peart WS, Barnes GR, Broughton P. Adverse reactions to bendrofluzide and propranolol for the treatment of mild hypertension. Report of Medical Research Council Working Party on Mild to Moderate Hypertension. <i>Lancet</i> 1981;2(8246):539-43 Bird AS, Blizard RA, Mann AH. Treating hypertension in the older person: an evaluation of the association of blood pressure level and its reduction with cognitive performance. <i>J Hypertens</i> 1990;8(2):147-52.
13	Ogihara et al ⁵⁰	Ogihara T, Kuramoto K. Effect of long-term treatment with antihypertensive drugs on quality of life of elderly patients with hypertension: A double-blind comparative study between a calcium antagonist and a diuretic. <i>Hypertension Research Clinical & Experimental</i> 2000;23(1):33-7
14	Potempa et al ⁵¹	Potempa K, Babich K, Fruh S, Fogg L. Blood pressure and mood responses in hypertensive patients on antihypertensive medications. <i>J Am Acad Nurse Pract</i> 1993;5(5):211-8
15	SHELL ³¹	Malacco E, Mancina G, Rappelli A, Menotti A, Zuccaro MS, Coppini A, et al. Treatment of isolated systolic hypertension: the SHELL Study results. <i>Blood Press</i> 2003;12(3):160-7
16	SHEP ³²	SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. <i>JAMA</i> 1991;265(24):3255-64
17	Slovick et al ⁵²	Slovick DI, Fletcher AE, Daymond M, Mackay EM, VandenBurg MV, Bulpitt CJ. Quality of life and cognitive function with a diuretic compared with a beta blocker: A randomized controlled trial of bendrofluzide versus diltiazem in elderly hypertensive patients. <i>Cardiol Elderly</i> 1995;3(2):139-45

No	Trial	Reference
18	Starr et al ⁵³	Starr JM, Whalley LJ, Deary IJ. The effects of antihypertensive treatment on cognitive function: results from the HOPE study. <i>J Am Geriatr Soc</i> 1996;44(4):411-5
19	Suzuki et al ⁵⁴	Suzuki H, Tominaga T, Kumagai H, Saruta T. Effects of first-line antihypertensive agents on sexual function and sex hormones. <i>J Hypertens</i> 1988;6(Suppl 4):S649-S651
20	Tedesco et al ⁵⁵	Tedesco MA, Ratti G, Mennella S, Manzo G, Grieco M, Rainone AC, et al. Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. <i>Am J Hypertens</i> 1999;12(11 Pt 1):1130-4
21	TOMHS ^{56,116,117}	1. Neaton JD, Grimm RH, Prineas RJ, Stamler J, Grandits GA, Elmer PJ, et al. Treatment of Mild Hypertension Study. Final results. <i>JAMA</i> 1993;270(6):713-24 2. Grimm, R.H., Grandits, G.A., Cutler, J.A., et al. Relationships of quality-of-life measures to long-term lifestyle and drug treatment in the Treatment of Mild Hypertension. <i>Arch Intern Med</i> 1997;157(6):638-48 3. Grimm RH, Grandits GA, Prineas RJ, McDonald RH, Lewis CE, Flack JM, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS). <i>Hypertension</i> 1997;29(1 Pt 1):8-14
22	VA-II ³⁵	Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. <i>JAMA</i> 1970;213(7):1143-52
23	VA-NHLBI ³⁶	Mitchell Perry H, Goldman AI, Lavin MA, Schanper HW, Fitz AE, Frohlich ED, et al. Evaluation of drug treatment in mild hypertension: VA-NHLBI feasibility trial. Plan and preliminary results of a two-year feasibility trial for a multicenter intervention study to evaluate the benefits versus the disadvantages of treating mild hypertension. Prepared for the Veterans Administration-National Heart, Lung, and Blood Institute Study Group for Evaluating Treatment in Mild Hypertension. <i>Ann N Y Acad Sci</i> 1978;304:267-92
24	Vanmolkot et al ⁵⁷	Vanmolkot FH, de Hoon JN, van de Ven L, Van Bortel LM. Impact of antihypertensive treatment on quality of life: comparison between bisoprolol and bendrofluzide. <i>J Hum Hypertens</i> 1999;13(8):559-63
25	VHAS ³⁷	Zanchetti A, Rosei EA, Dal Palù C, Leonetti G, Magnani B, Pessina A. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. <i>J Hypertens</i> 1998;16(11):1667-76
26	Wassertheil-Smoller et al ⁵⁸	Wassertheil-Smoller S, Blaufox MD, Oberman A, Davis BR, Swencionis C, Knerr MO, et al. Effect of antihypertensives on sexual function and quality of life: the TAIM Study. <i>Ann Intern Med</i> 1991;114(8):613-20.
Trials related to question 2: Economic analyses		
1	Baio et al ⁸⁹	Baio G, Degli Esposti L, Degli Esposti E, Saragoni S, Capone A, Russo P, et al. Bayesian cost-effectiveness analysis based on the persistence with antihypertensive treatment. <i>Expert Rev Pharmacoecon Outcomes Res</i> 2003;3(3):227-36.
2	Burns ⁸⁵	Burns R. Cost effectiveness in the treatment of hypertension. <i>Clin Geriatr Med</i> 1989;5(4):829-40.
3	Chen et al ⁸⁶	Chen GJ, Ferrucci L, Moran WP, Pahor M. A cost-minimization analysis of diuretic-based antihypertensive therapy reducing cardiovascular events in older adults with isolated systolic hypertension. <i>Cost Eff Resour Alloc</i> 2005;3(1):2. <i>Cost Eff Resour Alloc</i> 2005;3(1):2.

No	Trial	Reference
4	Edelson et al ⁸¹	Edelson JT, Weinstein MC, Tosteson AN, Williams L, Lee TH, Goldman L. Long-term cost-effectiveness of various initial monotherapies for mild to moderate hypertension. <i>JAMA</i> 1990;263(3):407-13.
5	Fretheim et al ⁹²	Fretheim A, Aaserud M, Oxman AD. The potential savings of using thiazides as the first choice antihypertensive drug: cost-minimisation analysis. <i>BMC Health Serv Res</i> 2003;3(1). Available: http://www.biomedcentral.com/1472-6963/3/18 (accessed 2005 Feb 9).
6	Grimm ¹¹⁸	Grimm RH. Epidemiological and cost implications of antihypertensive treatment for the prevention of cardiovascular disease. <i>J Hum Hypertens</i> 1989;3 Suppl 2:55-60.
7	Hilleman et al ⁹⁰	Hilleman DE, Mohiuddin SM, Lucas BD, Stading JA, Stoysich AM, Ryschon K. Cost-minimization analysis of initial antihypertensive therapy in patients with mild-to-moderate essential diastolic hypertension. <i>Clin Ther</i> 1994;16(1):88-102.
8	Hoerger et al ¹¹⁹	Hoerger TJ, Bala MV, Eggleston JL, Hilleman DE, Neutel JM, Tomondy PA. A comparative cost-effectiveness study of three drugs for the treatment of mild-to-moderate hypertension. <i>P & T</i> 1998;23(5):245-67.
9	Johannesson et al ⁸³	Johannesson M, Wikstrand J, Jönsson B, Berglund G, Tuomilehto J. Cost-effectiveness of antihypertensive treatment: metoprolol versus thiazide diuretics. <i>Pharmacoeconomics</i> 1993;3(1):36-44.
10	Johannesson ⁸²	Johannesson M. The cost-effectiveness of hypertension treatment in Sweden: an analysis of the criteria for intervention and the choice of drug treatment. <i>J Hum Hypertens</i> 1996;10 Suppl 2:S23-S26.
11	Kawachi and Malcolm ⁷⁹	Kawachi I, Malcolm LA. The cost-effectiveness of treating mild-to-moderate hypertension: a reappraisal. <i>J Hypertens</i> 1991;9(3):199-208.
12	Linjer et al ⁹¹	Linjer E, Hedner TT, Jönsson B, Ekblom T, Lindholm LH, Dahlöf B, et al. Cost analysis of different pharmacological treatment strategies in elderly hypertensives. <i>Blood Press</i> 2005;14(2):107-13.
13	Marshall ¹²⁰	Marshall T. Coronary heart disease prevention: insights from modelling incremental cost effectiveness. <i>BMJ</i> 2003;327(7426):1264.
14	Nordmann et al ⁷⁸	Nordmann AJ, Krahn M, Logan AG, Naglie G, Detsky AS. The cost effectiveness of ACE inhibitors as first-line antihypertensive therapy. <i>Pharmacoeconomics</i> 2003;21(8):573-85.
15	Pearce et al ⁸⁷	Pearce KA, Furberg CD, Psaty BM, Kirk J. Cost-minimization and the number needed to treat in uncomplicated hypertension. <i>Am J Hypertens</i> 1998;11(5):618-29.
16	Plans-Rubio ⁸⁰	Plans-Rubió P. Cost-effectiveness analysis of treatments to reduce cholesterol levels, blood pressure and smoking for the prevention of coronary heart disease: evaluative study carried out in Spain. <i>Pharmacoeconomics</i> 1998;13(5 Pt 2):623-43.
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APPENDIX 7: EXCLUDED REPORTS

Reports excluded for Question 1:

Comparators not relevant

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APPENDIX 8A: CHARACTERISTICS OF TRIALS INVOLVING THIAZIDE DIURETICS VERSUS PLACEBO OR NO TREATMENT AND OTHER ANTIHYPERTENSIVE DRUG CLASSES

Trial (year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
ALLHAT, 2002 ¹²	Randomized, double-blind, active-controlled trial	US, Canada, Puerto Rico, US Virgin Islands (623 centres)	National Heart, Lung, and Blood Institute; study medications supplied by Pfizer, AstraZeneca, and Bristol-Myers Squibb; financial support from Pfizer	Chlorthalidone	15,255	1 yr: 1,401 5 yrs: 9,045	4.9 ± 1.4 (SD)
				Amlodipine	9,048	1 yr: 833 5 yrs: 5,279	
				Lisinopril	9,054	1 yr: 896 5 yrs: 5,449	
ANBP-1, 1980 ¹³	Randomized controlled trial; patients and outcome assessors blinded	Australia (4 centres)	National Health and Medical Research Council of Australia, Life Insurance Medical Research Fund of Australia and New Zealand, Victorian Government, Clive and Vera Ramaciotti Foundations, and the Raine Medical Research Foundation of Western Australia	CLTZ	1,721	583	4.06
				Placebo	1,706	626	4.03
ANBP-2, 2003 ¹⁴	Randomized open-label trial with blinded assessments of end points	Australia (1,594 family practices)	Australian Commonwealth Department of Health and Aging; National Health and Medical Research Council of Australia; Merck Sharp & Dohme, Australia	HCTZ (recommended) or other diuretic	3,039	101	Median: 4.1
				Enalapril (recommended) or other ACE inhibitor	3,044	66	

Trial (year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
ANBPS, 1981 ¹⁵	Randomized placebo-controlled trial; blinding not reported	Australia (no. of centres NR)	National Health and Medical Research Council of Australia; Life Insurance Medical Research Fund of Australia and New Zealand; Victoria Government; Clive and Vera Ramaciotti Foundations; Raine Medical Research Foundation of Western Australia	CLTZ	293	96	3.93
				Placebo	289	100	3.81
Barraclough, 1973 ¹⁶	Randomized, single-blind, controlled trial	Britain (2 centres)	Not stated. Drugs supplied by Glaxo Ltd., Merck Sharp and Dohme Ltd., and Roche Products Ltd.	BFTZ	58	3	NR. Patients stayed in trial from one month to four years
				Ca lactate	58	14	
Carter, 1970 ¹⁷	Randomized controlled trial; blinding not reported	Britain (1 centre)	North West Metropolitan Regional Hospital Board	Thiazide diuretics	50	1	4
				Untreated	49	1	
EWPHE, 1985 ¹⁸	Randomized, double blind, placebo-controlled trial	Norway, The Netherlands, Belgium, France, England, Finland, Scotland, Ireland, Germany, Portugal ¹²¹ (?19 centres)	Belgian National Research Foundation; Belgian Hypertension Committee; Merck, Sharp and Dohme; Smith, Kline and French	HCTZ + triamterene	416	169	4.69
				Placebo	424	122	4.63
HAPPY, 1987 ¹⁹	Randomized open label trial	Belgium, Canada, Denmark, Finland, France, Germany, Greece, Great Britain,	AB Hässle, Mölndal, a subsidiary of AB Astra, Sweden and ICI, UK	BFTZ or HCTZ	3,272	291	3.8

Trial (year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
		Holland, Iceland, Italy, Norway, Sweden, Czechoslovakia, US (184 centres)		Atenolol or Metoprolol	3,297	260	
HSCSG, 1974 ²⁰	Randomized, double-blind, controlled trial	US (10 centres)	National Institute of Neurological Diseases and Stroke	MCTZ + deserpidine	233	NR	NR
				Placebo	219		
HYVET, 2003 ²¹	Randomized, controlled, open pilot trial	UK, Bulgaria, Finland, Romania, Spain, Lithuania, Ireland, Poland, Greece, Serbia (no. of centres NR)	British Heart Foundation	Diuretic (usually BFTZ)	426	10	1.1
				ACE inhibitor (usually lisinopril)	431	7	
				No treatment	426	10	
INSIGHT, 2000 ²²	Randomized, controlled, double-blind trial	Sweden, Norway, Denmark, France, UK, Israel, Germany, Switzerland (703 centres)	Bayer AG	Co-amilozone (HCTZ + amiloride)	3,286	1,170	4
				Nifedipine	3,289	1,391	
MAPHY, 1988 ^{23,113}	Randomized, open, controlled trial	Sweden, Canada, Czechoslovakia, Denmark, Finland, Greece, the Netherlands, Norway, Iceland, Italy, UK (66 centres)	Swedish National Association Against Heart and Chest Diseases and the Astra Cardiovascular Research Laboratories	HCTZ or BFTZ	1,625	NR	5 Max: 10.8
				Metoprolol	1,609		
MIDAS, 1996 ²⁴	Randomized, double-blind, positive-controlled trial	US (9 centres)	Supported in part by Sandoz Research Institute, Sandoz Pharmaceuticals, NJ	HCTZ	441	NR. 18.3% off study medication	3
				Isradipine	442	NR. 19.8% off study medication	

Trial (year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
MRC-Mild, 1985 ²⁵	Randomized controlled trial, with blinded assessments of end-points	England, Scotland, Wales (190 centres)	Imperial Chemical Industries Ltd provided financial support, propranolol and placebo; CIBA Laboratories provided guanethidine; Merck Sharp and Dohme Ltd provided a mobile screening unit and funds for its staffing and supplies of methyldopa.	BFTZ	4,297	1,641	Max: 5.5
				Propranolol	4,403	1,807	
				Placebo	8,654	3,779	
MRC – Old, 1992 ²⁶	Randomized, placebo controlled, single blind trial	England, Scotland, Wales (22 centres)	Merck Sharp and Dohme supplied Moduret and placebo; Imperial Chemical Industries supplied Tenormin and placebo; Bayer supplied Adalat	Amiloride or HCTZ	1,081	161	5.8
				Atenolol	1,102	345	
				Placebo	2,213	257	
NICS – EH, 1999 ²⁷	Randomized controlled trial. Patients and end-point assessments were blinded	Japan (no. of centres NR)	NR	TMTZ	210	20	Median: 3.9, Max: 5
				Nicardipine	204	22	Median: 4.6, Max 5
OSLO, 1980 ²⁸	Randomized controlled trial with blinded assessment	Norway (no. of centres NR)	NR	HCTZ	406	NR	5.5
				No treatment	379		
PATs, 1995 ²⁹	Randomized, placebo-controlled, double-blinded trial	China (44 centres)	World Bank Office, Ministry of Public Health (China); Clinical Trial Service Unit of Oxford University (UK)	Indapamide	2,841	162	2
				Placebo	2,824	150	

Trial (year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
PHS, 1977 ³⁰	Randomized, placebo-controlled, single-blind trial	US (no. of centres NR)	National Institutes of Health, US	Chlorothiazide	193	88	> 7 years (range: 78-108 months)
				Placebo	196	119	
SHELL, 2003 ³¹	Randomized controlled trial; double-blind in 12 centres for the first year only; open-label in other centres for entire trial	Italy (no. of centres NR. Patients recruited from 134 centres)	Laboratori Guidotti	Chlorthalidone	940	NR	Median: 2.7 Max: 5
				Lacidipine	942		
SHEP, 1991 ³²	Randomized, double-blind, placebo-controlled trial	US (16 centres)	National Heart, Lung, and Blood Institute and the National Institute on Aging; drugs supplied by the Lemmon Co., Wyeth Laboratories/Ayerst Laboratories, AH Robins Co., and Stuart Pharmaceuticals	Chlorthalidone	2,365	307	4.5
				Placebo	2,371	166	
SHEP-PS, 1989 ³³	Randomized, double-blind, placebo-controlled trial	US (?5 centres)	National Heart, Lung and Blood Institute; National Institute of Aging; National Institute of Mental Health; National Institutes of Health	Chlorthalidone	443	NR	2.8
				Placebo	108		
VA I, 1967 ³⁴	Randomized, double-blind, placebo-controlled trial	US (16 centres)	NR	HCTZ + reserpine 70+ hydralazine HCl	73	5	1.7 Max: 2
				Placebo	70	7	1.3 Max: 2

Trial (year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
VA II, 1970 ³⁵	Randomized, double-blind, placebo-controlled trial	US (17 centres)	NR	HCTZ + reserpine + hydralazine HCl	186	29	3.2 Max: 5.5
				Placebo	194	27	3.3 Max: 5.5
VA-NHLBI, 1978 ³⁶	Randomized, double-blind, placebo-controlled feasibility trial	US (4 centres)	Veterans Administration; National Heart, Lung and Blood Institute; National Institutes of Health; Department of Health, Education and Welfare	Chlorthalidone	508	98	Max: 2
				Placebo	504	104	
VHAS, 1997 ³⁸	Randomized, double-blind for 6 months, then open parallel-group trial continuation	Italy (no. of centres NR)	NR	Chlorthalidone	707	162	Max: 2
				Verapamil	707	153	

TZD: thiazide/diuretics; BB: β -blockers; AB: α -blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; HCTZ: hydrochlorothiazide; BFTZ: bendroflumethiazide or bendrofluazide; TMTZ: trichlormethiazide; CLTZ: chlorothiazide; MCTZ: methyclothiazide

APPENDIX 8B: CHARACTERISTICS OF TRIALS INVOLVING QOL

Study (Author, year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
ALPINE ³⁹	Randomized, double-blind controlled trial	Sweden	Department of Public Health and Clinical Medicine, Umeå University, Sweden; AstraZeneca R&D, Sweden; Hässle Läkemedel AB, Sweden	HCTZ	196	14	NR; trial was 1 year
				Candesartan	197	16 + 1 excluded due to no efficacy data	
Bird et al ⁴⁰	Single-blind, randomized, placebo-controlled trial	England, Scotland, Wales	Medical Research council (UK) and Wellcome Trust	Moduretic	2,446	NR	NR; trial follow-up was 5 years
				Atenolol			
				Placebo			
Boissel et al ⁴¹	Randomized	Canada, France	Searle France, Merck Sharpe & Dohme Chibret, Merck Clevenot and Laboratories Knoll France	Altizide or spironolactone	164	208	1
				Enalapril	164		
				Bisoprolol	162		
				Verapamil	163		
Chang et al, 1991 ⁴²	Randomized, placebo-controlled trial	US	National Institutes of Health, Bethesda Md	Diuretic	153 completed questionnaire	7 + 1 death	NR; trial was 2 months
				Placebo	23 completed questionnaire	6 + 1 death	
EWPHE, 1985 ¹⁸	Randomized, double blind, placebo-controlled trial	Norway, The Netherlands, Belgium, France, England, Finland, Scotland, Ireland, Germany, Portugal ¹²¹ (?19 centres)	Belgian National Research Foundation; Belgian Hypertension Committee; Merck, Sharp and Dohme; Smith, Kline and French	HCTZ + triamterene	416	169	4.69
				Placebo	424	122	4.63

Study (Author, year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
Glick et al, 1990 ⁴⁴	Randomized	US	Ciba-Geigy, Smith Kline & French, Merck Sharpe & Dohme, and E.R. Squibb & Company	HCTZ-triamterene	34	NR	NR; trial was 4 months
				Captopril	13		
				Metoprolol	17		
				Methyldopa	10		
HAPPY, 1987 ¹⁹	Randomized, open-label trial	Belgium, Canada, Denmark, Finland, France, Germany, Greece, Great Britain, Holland, Iceland, Italy, Norway, Sweden, Czechoslovakia, US (184 centres)	AB Hässle, Mölndal, a subsidiary of AB Astra, Sweden and ICI, UK	BFTZ or HCTZ	3,272	291	3.8
				Atenolol or Metoprolol	3,297	260	
Lacourciere et al, 1988 ⁴⁵	Randomized trial	Canada	NR	Indapamide	14	0	0.2
				Captopril	16		
Malmqvist et al, 2000 ⁴⁶	Randomized, double blind trial	Sweden (56 centres)	Astra Hassle AB	HCTZ	143	100	NR; trial was 12 weeks
				Enalapril	146		
				Candesartan	140		
Martin et al, 1994 ⁴⁷	Randomized trial	Spain	NR	HCTZ	591	12	0.5
				Captopril	591	23	
MRC-Mild, 1981 ⁴⁹	Randomized controlled trial, with blinded assessments of end-points	England, Scotland, Wales (190 centres)	Imperial Chemical Industries Ltd provided financial support, propranolol and placebo; CIBA Laboratories provided guanethidine; Merck Sharp and Dohme Ltd provided a mobile screening unit and funds for its staffing and supplies of methyldopa.	BFTZ	4,297	1,641	Max: 5.5
				Propranolol	4,403	1,807	
				Placebo	8,654	3,779	

Study (Author, year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
Metelitsa et al, 1996 ⁴⁸ (1996)	Open, comparative-controlled, randomized trial	Russia, Ukraine, Azerbaijan (7)	Bristol-Myers Squibb	HCTZ	83	NR	NR; maximum 0.7
				Captopril	86		
				Nifedipine	89		
				Propranolol	87		
NICS-EH, 2000 ⁵⁰	Randomized, double-blind, comparative study	Japan (108)	NR	Trichlormethiazide	214	54	NR; trial was 5 years
				Nicardipine	215	39	
Potempa et al, 1993 ⁵¹	Randomized, 3/2 factorial repeated measures experimental design	US (1)	NR	HCTZ	12	NR	.08
				Pindolol	16		
				Propranolol	13		
SHELL, 2003 ³¹	Randomized controlled trial; double-blind in 12 centres for the first year only; open-label in other centres for entire trial	Italy (no. of centres NR. Patients recruited from 134 centres)	Laboratori Guidotti	Chlorthalidone	940	NR	Median: 2.7 Max: 5
				Lacidipine	942		
SHEP, 1991 ³²	Randomized, double-blind, placebo-controlled trial	US (16 centres)	National Heart, Lung, and Blood Institute and the National Institute on Aging; drugs supplied by the Lemmon Co., Wyeth Laboratories/Ayerst Laboratories, AH Robins Co., and Stuart Pharmaceuticals	Chlorthalidone	2,365	307	4.5
				Placebo	2,371	166	
Slovick et al, 1995 ⁵²	Randomized, controlled,	UK (multicentre)	Schering Plough	Bendrofluazide	57	12	NR; trial had 20-wk

Study (Author, year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
	double-blind, parallel group, multicentre study			Dilevalol	57	15	maintenance phase
HOPE, 1996 ⁵³	Randomized, double-blind trial	UK (1)	Bristol-Meyers Squibb	Bendrofluazide	40	12	NR; trial was 24 wks
				Captopril	41	12	
Suzuki et al, 1988 ⁵⁴	Randomized trial	Japan	NR	Trichloromethiazide	39	NR	1
				Atenolol	39		
				Captopril	39		
				Nifedipine	39		
Tedesco et al, 1999 ⁵⁵	Randomized, double-blind study	Italy	NR	HCTZ	27	0	2.2
				Losartan	42		
TOMHS, 1993 ⁵⁶	Randomized, double-blind, placebo-controlled trial	US (4)	National Heart, Lung and Blood Institute; National Institutes of Health; Pfizer; Merck Sharp & Dohme Research Laboratories. Additionally, drugs supplied by Boehringer Ingelheim Pharmaceuticals; Pfizer Inc; Wyeth-Ayerst Laboratories	Chlorthalidone	136	NR; 5 had no follow-up visits	Median: 4.4
				Acebutolol	132		
				Amlodipine	131		
				Doxazosin	134		
				Enalapril	135		
				Placebo	234		
VA II, 1970 ³⁵	Randomized, double-blind, placebo-controlled trial	US (17 centres)	NR	HCTZ + reserpine + hydralazine HCl	186	29	3.2 Max: 5.5
				Placebo	194	27	3.3 Max: 5.5
VA-NHLBI, 1978 ³⁶	Randomized, double-blind, placebo-controlled feasibility trial	US (4 centres)	Veterans Administration; National Heart, Lung and Blood Institute; National Institutes of Health; Department of Health, Education and Welfare	Chlorthalidone	508	98	Max: 2
				Placebo	504	104	

Study (Author, year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
Vanmolkot et al, 1999 ⁵⁷	Randomized, double-blind, multicentre, two-way crossover trial	The Netherlands (6)	E Merck	Bendrofluazide	81	2	NR; length of trial was 24-28 wks
				Bisoprolol			
VHAS, 1997 ³⁸	Randomized, double-blind for 6 months, then open parallel-group trial continuation	Italy (no. of centres NR)	NR	Chlorthalidone	707	162	Max: 2
				Verapamil	707	153	
TAIM, 1991 ³⁸	Randomized, placebo-controlled, multicentre trial	US (3)	National Heart, Lung and Blood Institute; drugs supplied by ICI Pharmaceuticals and AH Robins	Chlorthalidone	227	NR	NR; length of trial was 6 months

APPENDIX 8C: CHARACTERISTICS OF TRIALS RELATED TO BP TARGET (MODERATE VERSUS INTENSIVE LOWERING OF BP)

Study (Author, year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow- up (years)
AASK, 2002 ⁵⁹	Randomized 3x2 factorial trial; participants and investigators blinded to drug but not BP goal	US (21)	National Institute of Diabetes and Digestive and Kidney Diseases; General Clinical Research Center; National Institutes of Health; Office of Research in Minority Health; Pfizer Inc.; AstraZeneca Pharmaceuticals; and King Pharmaceuticals Inc.	Usual BP (Arterial pressure: 102-107 mmHg)	554	NR	NR; length of follow- up 3 to 6.4 yrs
				Lower BP (Arterial pressure: ≤ 92 mmHg)	540		
ABCD-H, 2000 ⁶⁰	Randomized trial; patients blinded to drug	US (1)	Aventis Pharma	Moderate (DBP 80-89 mmHg)	233	NR	NR; length of follow- up 5 yrs
				Intensive (DBP 75 mmHg)	237		
ABCD-N, 2002 ⁶¹	Randomized, single-blind, controlled trial; patients blinded to drug	US (1)	Bayer Pharmaceutical Co.; National Institute of Diabetes, Digestive, and Kidney Diseases	Moderate (DBP 80-90 mmHg)	243	NR	5.3
				Intensive (DBP decrease of 10 mmHg)	237		
CSG, 1999 ⁶²	Randomized trial	US (17)	Supported in part by a grant from Hoechst-Roussel Pharmaceuticals International	Mean arterial pressure: $\leq$ 92 mmHg	66	NR	2
				Mean arterial pressure: 100-107 mmHg	63		
HOT, 1998 ⁶³	Randomized, open with blinded endpoint	26 countries in Europe, North and South America, and	Astra AB, Sweden; Astra Merck Inc., USA; TEVA, Israel; Hoechst, Argentina	DBP ≤ 90 mmHg	6264	169	3.8
				DBP ≤ 85 mmHg	6264	157	

Study (Author, year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow-up (years)
	evaluation trial	Asia		DBP $\leq$ 80 mmHg	6262	165	
Ikeda et al, 2002 ⁶⁴	Randomized trial	Japan (1)	NR	BP < 130/80 mmHg	28	NR	2
				BP < 120/75 mmHg	28		
MDRD, 2005 ⁶⁵	Randomized, controlled trial	US (15)	National Institutes of Diabetes and Digestive and Kidney Diseases	Usual (age $\leq$ 60 years: arterial BP <107 mmHg (<140/90 mmHg); age > 60 years: arterial BP 113 mmHg)	408	NR	2.2
				Low (age $\leq$ 60 years: arterial BP < 92 mmHg (< 125/75 mmHg); age > 60 years: arterial BP 98 mmHg)	432		
REIN-2, 2005 ⁶⁶	Randomized, controlled, open, multicentre trial	Italy (29)	Supported in part by a grant from Aventis Pharma	Conventional BP (DBP < 90 mmHg)	168 (169 randomized; 1 never took study drugs)	NR	3
				Intensified BP (< 130/80 mmHg)	167 (169 randomized; 2 never took study drugs)		
Toto et al, 1995 ⁶⁷	Randomized, double-blind, 2x2 factorial, placebo-controlled trial	US (NR)	Merck, Sharp and Dohme. Medications provided by Merck Sharp and Dohme, Pfizer, Stuart Pharmaceutical, E.R. Squibb & Sons Inc., Marion Laboratories Inc.,	Conventional (DBP= 85-95 mmHg)	35	NR	3.4

Study (Author, year)	Study Design	Countries (no. of centres)	Sponsor	Treatment arms	No. of patients	Withdrawals	Mean length of follow- up (years)
			Boehringer Ingelheim Pharmaceuticals Inc, Smith Kline & French Laboratories, Hoechst- Roussel Pharmaceuticals Inc., CIBA-GEIGY Corp., Ayerst Laboratories, GEIGY Pharmaceuticals, and The Upjohn Co.	Strict BP (DBP= 65-80 mmHg)	42		

APPENDIX 9A: CHARACTERISTICS OF PATIENTS IN TRIALS INVOLVING THIAZIDE DIURETICS VERSUS PLACEBO/NO TREATMENT AND OTHER ANTIHYPERTENSIVE DRUG CLASSES

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
ALLHAT, 2002 ¹²	Chlorthalidone	15,255	66.9 (7.7)	53/47	White: 47 Black: 32 Hispanic: 16 Other: 5	Current: 22	36	26	90	29.7 (6.2)	146/84 (16/10); stage 1 or 2 hypertension
	Amlodipine	9,048	66.9 (7.7)	53/47	White: 48 Black: 32 Hispanic: 15 Other: 5	Current: 22	37	24	90	29.8 (6.3)	146/84 (16/10); stage 1 or 2 hypertension
	Lisinopril	9,054	66.9 (7.7)	54/46	White: 47 Black: 32 Hispanic: 16 Other: 5	Current: 22	35	25	90	29.8 (6.2)	146/84 (16/10); stage 1 or 2 hypertension
ANBP-1, 1980 ¹³	Chlorothiazide	1,721	50.4 (9.0)	63/37	NR	Current: 24	0	NR	0	NR	DBP: 100; mild hypertension
	Placebo	1,706	50.5 (8.9)	64/36	NR	Current: 26	0	NR	0	NR	DBP: 100; mild hypertension
ANBP-2 (Wing), 2003 ¹⁴	Hydrochlorothiazide (recommended) or other diuretic	3,039	72.0	50/50	NR	Ex-smoker: 46 Current: 7	8	8	62	27 (4)	167/91 (13/8); Grade 1: 20% Grade 2: 65% Grade 3: 15%
	Enalapril (recommended) or other ACE inhibitor	3,044	71.9	48/52	NR	Ex-smoker: 45 Current: 7	7	8	62	27 (4)	168/91 (13/8); Grade 1: 18% Grade 2: 66% Grade 3: 15%
	All	6,083	71.9	49/51	NR	Ex-smoker: 45 Current: 7	7	8	62	27 (4)	168/91 (13/8); Grade 1: 19% Grade 2: 66% Grade 3: 15%

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
ANBPS, 1981 ¹⁵	Chlorothiazide	293	63.6 (2.3)	55/45	NR	Current: 18	0	NR	0	NR	166.3/100.7 (14.9/4.0)
	Placebo	289	63.5 (2.3)	54/46	NR	Current: 17	0	NR	0	NR	163.9/100.4 (14.9/3.9)
Barraclough et al, 1973 ¹⁶	Bendrofluazide	58	Men: 54.4 Women: 55.7	40/60	NR	NR	NR	NR	0	NR	DBP: 110
	Ca lactate	58	Men: 55.2 Women: 56.5	47/53	NR	NR	NR	NR	0	NR	DBP: 109
Carter et al, 1970 ¹⁷	Thiazide diuretics	50	Range: 40-79	54/46	NR	NR	NR	NR	NR	NR	NR; DBP >110 or SBP >160
	Untreated	49	Range: 40-79	59/41	NR	NR	NR	NR	NR	NR	NR; DBP >110 or SBP >160
EWPHE, 1985 ¹⁸	Hydrochlorothiazide + triamterene	416	72 (8)	31/69	NR	NR	NR	NR	NR	NR	183/101 (17/7)
	Placebo	424	72 (8)	30/70	NR	NR	NR	NR	NR	NR	182/101 (16/7)
HAPPY, 1987 ¹⁹	Bendroflumethiazide or Hydrochlorothiazide	3,272	52.3	100/0	NR	Ex-smoker: 22 Current: 34	NR	NR	35% of all patients	27.1	166/107; mild to moderate hypertension
	Atenolol or Metoprolol	3,297	52.2	100/0	NR	Ex-smoker: 20 Current: 35	NR	NR		27.3	166/107; mild to moderate hypertension
HSCSG, 1974 ²⁰	Deserpidine + methyclothiazide	233	NR	60/40	White: 18 Black: 82	NR	NR	NR	NR	NR	NR
	Placebo	219	NR	58/42	White: 21 Black: 79	NR	NR	NR	NR	NR	NR

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
	All	452	59	59/41	White: 20 Black: 80	NR	NR	NR	NR	NR	167/100
HYVET, 2003 ²¹	Diuretic (usually bendrofluazide)	426	83.8 (3.3)	37/63	NR	Ex-smoker: 7 Current: 2	NR	NR	NR	25.3 (3.4)	181.5/99.6 (11.3/3.4)
	ACE inhibitor (usually lisinopril)	431	83.7 (3.0)	36/64	NR	Ex-smoker: 11 Current: 5	NR	NR	NR	25.5 (3.4)	181.9/99.6 (11.3/3.3)
	No treatment	426	83.8 (2.9)	37/63	NR	Ex-smoker: 8 Current: 5	NR	NR	NR	25.4 (3.7)	181.0/99.5 (11.5/3.6)
INSIGHT, 2000 ²²	Co-amilozone	3,286	NR	47/53	NR	Current: 28	21	6	NR	NR	NR
	Nifedipine	3,289	NR	46/54	NR	Current: 28	21	7	NR	NR	NR
	All	6,575	65 (6.5)	NR	NR	Current: 28	21	NR	NR	NR	173/99 (14/8), following 2-4 week placebo phase
MAPHY, 1988 ²³	Hydrochlorothiazide or bendroflumethiazide	1,625	52.6 (6)	100/0	NR	Current: 33	NR	NR	NR	27.1 (3.5)	166.8/107.5 (17/6)
	Metoprolol	1,609	52.6 (7)	100/0	NR	Current: 34	NR	NR	NR	27.3 (3.5)	166.9/107.6 (17/6)
MIDAS, 1996 ²⁴	Hydrochlorothiazide	441	58.7 (8.7)	76/24	White: 74 Black: 20 Other: 6	Ex-smoker: 40 Current: 21	NR	NR	75	27.6 (4.0)	148.9/96.2 (16.4/5.0)
	Isradipine	442	58.2 (8.3)	80/20	White: 71 Black: 23 Other: 6	Ex-smoker: 38 Current: 19	NR	NR	78	27.9 (4.0)	150.6/96.7 (16.8/5.2)
	All	883	58.5 (8.5)	78/22	White: 72 Black: 22 Other: 6	Ex-smoker: 39 Current: 20			76	27.8 (4.0)	149.7/96.5 (16.6/5.1)
MRC – Mild, 1985 ²⁵	Bendrofluazide	4,297	Men: 51 Women: 53	52/48	NR	Current: Men 32%; Women 27%	NR	NR	0	NR	Men: 158/98; Women: 165/99

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
	Propranolol	4,403	Men: 51 Women: 53	52/48	NR	Current: Men 30%; Women 25%	NR	NR	0	NR	Men: 158/98; Women: 165/99
	Placebo	8,654	Men: 51 Women: 53	52/48	NR	Current: Men 27%; Women 27%	NR	NR	0	NR	Men: 158/98; Women: 165/98
MRC – Old, 1992 ²⁶	Amiloride or hydrochlorothiazide	1,081	Men: 70.2; Women: 70.4	42/58	NR	Current: Men 22%; Women 14%	NR	NR	0	Men 26.1; Women 26.8	Men: 183/92; Women: 186/90
	Atenolol	1,102	Men: 70.3; Women: 70.4	41/59	NR	Current: Men 21%; Women 15%	NR	NR	0	Men 26.4; Women 26.8	Men: 183/91; Women: 186/91
	Placebo	2,213	Men: 70.2; Women: 70.4	42/58	NR	Current: Men 24%; Women 13%	NR	NR	0	Men 26.4; Women 26.6	Men: 183/91; Women: 186/90
NICS – EH, 1999 ²⁷	Trichlormethiazide	210	69.9 (6.4)	26/74	NR	Current: 9	NR	NR	65	23.8 (3.4)	172.6/93.4 (11.0/10.2)
	Nicardipine	204	69.7 (6.5)	40/60	NR	Current: 11	NR	NR	56	23.2 (2.9)	171.9/94.2 (12.9/10.2)
	All	414	69.8 (6.5)	33/67	NR	Current: 10	NR	NR	61	23.5 (3.1)	172.3/93.8 (11.9/10.2)
OSLO, 1980 ²⁸	Hydrochlorothiazide	406	45.3 (2.9)	100/0	NR	Current: 41	NR	NR	0 in preceding year	NR	156.2/97.4 (7.1/6.9)
	No treatment	379	45.2 (2.8)	100/0	NR	Current: 42	NR	NR	0 in preceding year	NR	155.3/96.2 (7.6/7.2)

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
PATS, 1995 ²⁹	Indapamide	2,841	60 (8)	72/28	NR	NR	NR	NR	NR	NR	154/93 (23/13); Hypertension was not an inclusion criterium
	Placebo	2,824	60 (8)	72/28	NR	NR	NR	NR	NR	NR	154/93 (24/13); Hypertension was not an inclusion criterium
PHS, 1977 ³⁰	Chlorothiazide	193	44.3	77/23	White: 72	Current: 46	NR	NR	44	NR	147.8/98.8 (14.5/6.6)
	Placebo	196	Men: 44.6; Women: 43.9	83/17	White: 72	Current: 47	NR	NR	61	NR	145.9/99.0 (13.1/8.3)
	All	389	44	NR	White: 72	Current: 47	NR	NR	52	NR	NR
SHELL, 2003 ³¹	Chlorthalidone	940	72.4 (7.6)	38/62	NR	Ex-smoker: 16 Current: 10	NR	NR	51	NR	178.2/86.8 (10.3/5.8); Isolated systolic hypertension
	Lacidipine	942	72.3 (7.5)	40/60	NR	Ex-smoker: 14 Current: 11	NR	NR	52	NR	178.1/86.9 (10.2/5.7); Isolated systolic hypertension
SHEP, 1991 ³²	Chlorthalidone	2,365	71.6 (6.7)	44/56	White: 86 Black: 14	Ex-smoker: 37 Current: 13	10	NR	33	27.5 (4.9)	170.5/76.7 (9.5/9.6)
	Placebo	2,371	71.5 (6.7)	43/57	White: 86 Black: 14	Ex-smoker: 38 Current: 13	10	NR	33	27.5 (5.1)	170.1/76.4 (9.2/9.8)
	All	4,736	71.6 (6.7)	43/57	White: 86 Black: 14	Ex-smoker: 37 Current: 13	10	NR	33	27.5 (5.0)	170.3/76.6 (9.4/9.7)
SHEP-PS, 1989 ³³	All (Chlorthalidone + Placebo)	551	72.1	37/63	White: 82	Current: 11	NR	NR	23	NR	172/75; Isolated systolic hypertension

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
VA I, 1967 ³⁴	Hydrochlorothiazide + reserpine 70+ hydralazine hydrochloride	73	50 (8.7)	100/0	White: 42 Black: 58	NR	11	NR	NR	NR	185.6/121.2 (15.4/5); Diastolic hypertension with no signs of accelerated hypertension
	Placebo	70	51.4 (10.8)	100/0	White: 50 Black: 50	NR	7	NR	NR	NR	186.8/121 (17.2/4.7); Diastolic hypertension with no signs of accelerated hypertension
VA II, 1970 ³⁵	Hydrochlorothiazide + reserpine + hydralazine hydrochloride	186	50.5	100/0	Black: 41	NR	NR	NR	NR	NR	162.1/103.8; Mild diastolic hypertension
	Placebo	194	52.0	100/0	Black: 42	NR	NR	NR	NR	NR	165.1/104.7; Mild diastolic hypertension
VA-NHLBI, 1978 ³⁶	All (Chlorthalidone + Placebo)	1,012	37.5	100/0	White: 75 Black: 25	NR	NR	NR	NR	NR	DBP 93.3; Mild diastolic hypertension
VHAS, 1997 ³⁸	Chlorthalidone	707	53.9 (7.0)	50/50	NR	Current: 19	NR	NR	NR	27.1 (4.1)	168.8/102.3 (10.5/5.0)
	Verapamil	707	54.5 (6.9)	48/52	NR	Current: 17	NR	NR	NR	27.1 (4.1)	169.1/102.2 (10.4/5.1)

APPENDIX 9B: CHARACTERISTICS OF PATIENTS IN TRIALS INVOLVING QOL

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
ALPINE, 2003 ³⁹	HCTZ	196	55.4 (9.6)	47/53	White: 99	Ex-smoker: 35 Current: 10	0	NR	95	28.1 (4.2)	155.0/97.0 (13.5/5.7); primary hypertension
	Candesartan	196	54.5 (9.4)	48/52	White: 100	Ex-smoker: 31 Current: 16	0	NR	94	27.8 (4.1)	154.7/96.8 (13.2/5.6); primary hypertension
Bird et al, 1990 ⁴⁰	Moduretic (HCTZ + amiloride)	2446	70.3 (2.7)	42/58	NR	NR	NR	NR	NR	NR	Age 65-69: 183.4/91.2 (12.7/11.4); Age 70-75: 184.7/89.8 (13.1/11.6); mild hypertension
	Atenolol										
Boissel et al, 1995 ⁴¹	Altizide or spironolactone	164	52.2	42/58	NR	NR	NR	NR	0	NR	166.8/101
	Enalapril	164	51.4	52/48							164.5/100.5
	Bisoprolol	162	50.5	43/57							167.4/101.1
	Verapamil	163	52.3	49/51							165.7/100.3
Chang et al, 1991 ⁴²	Diuretic	153	61.3 (0.6)	100/0	White: 78 Black: 12 Other: 10	Current: 15	NR	NR	63	NR	141.5/85.7 (1.3/0.7)
	Placebo	23	60.4 (1.8)	100/0	White: 74 Black: 9 Other: 18	Current: 17	NR	NR	57	NR	142.8/83.8 (2.8/2.1)
EWPHE, 1985 ¹⁸	Hydrochlorothiazide + triamterene	416	72 (8)	31/69	NR	NR	NR	NR	NR	NR	183/101 (17/7)
	Placebo	424	72 (8)	30/70	NR	NR	NR	NR	NR	NR	182/101 (16/7)

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
Glick et al, 1990 ⁴⁴	HCTZ-triamterene	34	Range: 30 - 65+	20/80	White: 20 Black: 75.5 Other: 5	NR	NR	NR	NR	NR	NR
	Captopril	13									
	Metoprolol	17									
	Methyldopa	10									
HAPPY, 1987 ¹⁹	Bendroflumethiazide or Hydrochlorothiazide	3,272	52.3	100/0	NR	Ex-smoker: 22 Current: 34	NR	NR	35% of all patients	27.1	166/107; mild to moderate hypertension
	Atenolol or Metoprolol	3,297	52.2	100/0	NR	Ex-smoker: 20 Current: 35	NR	NR		27.3	166/107; mild to moderate hypertension
Lacourciere et al, 1988 ⁴⁵	Indapamide	14	51 (2)	43/57	NR	NR	NR	NR	NR	NR	NR; mild to moderate essential hypertension
	Captopril	16	49 (2)	56/44	NR	NR	NR	NR	NR	NR	NR; mild to moderate essential hypertension
Malmqvist et al, 2000 ⁴⁶	HCTZ	143	57.5	0/100	NR	Current: 16	NR	NR	66	NR	NR, DBP: 95 - 115
	Enalapril	146	57.3	0/100		Current: 18			73		
	Candesartan	140	58.1	0/100		Current: 22			69		
Martin et al, 1994 ⁴⁷	HCTZ	591	NR	44/56	NR	NR	NR	NR	NR	NR	168.58/102.63 (15.71/9.36); mild to moderate essential arterial hypertension
	Captopril	591	NR	53/47	NR	NR	NR	NR	NR	NR	171.08/103.96 (16.91/9.23); mild to moderate essential arterial hypertension

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
Metelitsa et al, 1996 ⁴⁸	HCTZ	83	NR	100/0	NR	NR	NR	NR	NR	NR	155.2/101.3; stable mild to moderate arterial hypertension stages I-II (WHO criteria)
	Captopril	86	NR	100/0	NR	NR	NR	NR	NR	NR	DBP 103.3; stable mild to moderate arterial hypertension stages I-II (WHO criteria)
	Nifedipine	89	NR	100/0	NR	NR	NR	NR	NR	NR	SBP 160.5; stable mild to moderate arterial hypertension stages I-II (WHO criteria)
	Propranolol	87	NR	100/0	NR	NR	NR	NR	NR	NR	NR; stable mild to moderate arterial hypertension stages I-II (WHO criteria)
MRC – Mild, 1981 ⁴⁹	Bendrofluazide	4,297	Men: 51 Women: 53	52/48	NR	Current: Men 32%; Women 27%	NR	NR	0	NR	Men: 158/98; Women: 165/99
	Propranolol	4,403	Men: 51 Women: 53	52/48	NR	Current: Men 30%; Women 25%	NR	NR	0	NR	Men: 158/98; Women: 165/99
	Placebo	8,654	Men: 51 Women: 53	52/48	NR	Current: Men 27%; Women 27%	NR	NR	0	NR	Men: 158/98; Women: 165/98

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
			en: 53								
NICS-EH, 2000 ⁵⁰	Trichlormethiazide	160	70 (7)	26/74	NR	Current: 8	NR	NR	NR	NR	172/93 (11/10); mild to moderate hypertension
	Nicardipine	176	70 (7)	39/61	NR	Current: 10	NR	NR	NR	NR	172/94 (13/13); mild to moderate hypertension
Potempa et al, 1993 ⁵¹	HCTZ	12	52 (15.3)	55/45	White: 64 Black: 36	NR	NR	NR	NR	28 (calculated from ht and wt)	145/101 (14.8/5.2); essential hypertension
	Pindolol	16	51 (9.7)	63/37	White: 56 Black: 44	NR	NR	NR	NR	30 (calculated from ht and wt)	144/99 (15.0/8.1); essential hypertension
	Propranolol	13	49 (11.9)	85/15	White: 69 Black: 31	NR	NR	NR	NR	31.3 (calculated from ht and wt)	156/100 (23.3/7.5); essential hypertension
SHELL, 2003 ³¹	Chlorthalidone	940	72.4 (7.6)	38/62	NR	Ex-smoker: 16 Current: 10	NR	NR	51	NR	178.2/86.8 (10.3/5.8); isolated systolic hypertension
	Lacidipine	942	72.3 (7.5)	40/60	NR	Ex-smoker: 14 Current: 11	NR	NR	52	NR	178.1/86.9 (10.2/5.7); isolated systolic hypertension
SHEP, 1991 ³²	Chlorthalidone	2,365	71.6 (6.7)	44/56	White: 86 Black: 14	Ex-smoker: 37 Current: 13	10	NR	33	27.5 (4.9)	170.5/76.7 (9.5/9.6)
	Placebo	2,371	71.5 (6.7)	43/57	White: 86 Black: 14	Ex-smoker: 38 Current: 13	10	NR	33	27.5 (5.1)	170.1/76.4 (9.2/9.8)

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
	All		71.6 (6.7)	43/57	White: 86 Black: 14	Ex-smoker: 37 Current: 13	10	NR	33	27.5 (5.0)	170.3/76.6 (9.4/9.7)
Slovick, 1995 ⁵²	Bendrofluazide	54	72.8 (5.1)	32/68	NR	NR	NR	NR	NR	NR	183.2/101.4 (181.8/102.7); uncomplicated essential hypertension
	Dilevalol	52	73.3 (5.7)	37/63	NR	NR	NR	NR	NR	NR	180.2/100.6 (175.6/101.3); uncomplicated essential hypertension
Starr et al, 1996 ⁵³	Bendrofluazide	35	76.1	NR	NR	NR	NR	NR	0	NR	191/101; mild to moderate hypertension
	Captopril	34									
Suzuki, 1988 ⁵⁴	Trichloromethiazide	156	Range: 22-55	100/0	100% Japanese	NR	NR	NR	NR	NR	Median DBP: 95-100; uncomplicated essential hypertension
	Atenolol										
	Captopril Nifedipine										
Tedesco et al, 1999 ⁵⁵	HCTZZ	27	Range: 32-70	52/48	NR	30	NR	NR	59	26 (3)	151/94 (9/5); uncomplicated mild to moderate essential hypertension
	Losartan	42	Range: 30-73	52/48	NR	35	NR	NR	61	26.7 (4)	
TOMHS, 1993 ⁵⁶	Chlorthalidone	136	55.2	64/36	Black: 23	NR	NR	NR	60	NR	140.5/90.4; mild hypertension
	Acebutolol	132	54.6	69/31	Black: 20	NR	NR	NR	61	NR	140.2/90.7; mild hypertension
	Amlodipine Maleate	131	53.8	59/41	Black: 14	NR	NR	NR	61	NR	138.1/90.9; mild hypertension

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
	Doxazosin Mesylate	134	54.8	60/40	Black: 19	NR	NR	NR	61	NR	140.8/90.6; mild hypertension
	Enalapril Maleate	135	55.3	57/43	Black: 20	NR	NR	NR	61	NR	140.8/90.2; mild hypertension
	Placebo	234	54.9	62/38	Black: 21	NR	NR	NR	61	NR	141.1/90.5; mild hypertension
VA II, 1070 ³⁵	Hydrochlorothiazide + reserpine + hydralazine hydrochloride	186	50.5	100/0	Black: 41	NR	NR	NR	NR	NR	162.1/103.8; mild diastolic hypertension
	Placebo	194	52.0	100/0	Black: 42	NR	NR	NR	NR	NR	165.1/104.7; mild diastolic hypertension
VA-NHLBI, 1978 ³⁶	All (Chlorthalidone + Placebo)	1,012	37.5	100/0	White: 75 Black: 25	NR	NR	NR	NR	NR	DBP 93.3; mild diastolic hypertension
Vanmolkot, 1999 et al ⁵⁷	Bendrofluazide	81	61 (24)	42/58	NR	Non-smoker: 37 Ex-smoker: 20 Current: 22	NR	NR	56	25.4 (calculated from ht and wt)	160/103 (2/1); mild to moderate hypertension
	Bisoprolol										
VHAS, 1997 ³⁸	Chlorthalidone	707	53.9 (7.0)	50/50	NR	Current: 19	NR	NR	NR	27.1 (4.1)	168.8/102.3 (10.5/5.0)
	Verapamil	707	54.5 (6.9)	48/52	NR	Current: 17	NR	NR	NR	27.1 (4.1)	169.1/102.2 (10.4/5.1)
Wassertheil-Smoller, 1991 ⁵⁸	Chlorthalidone	227	49	56/44	White: 68	NR	0	NR	67	NR	NR; DBP 90-100
	Atenolol	238									
	Placebo	232									

APPENDIX 9C: CHARACTERISTICS OF PATIENTS IN TRIALS RELATED TO BP TARGET (MODERATE VERSUS INTENSIVE LOWERING OF BP)

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
AASK, 2002 ⁵⁹	Usual BP (Arterial pressure: 102-107 mmHg)	554	54.7 (10.4)	60/40	Black: 100	NR	0	NR	97.5	NR	149/95 (23/14); arterial: 113 (15); diastolic hypertension
	Lower BP (Arterial pressure: ≤ 92 mmHg)	540	54.5 (10.9)	62/38	Black: 100	NR	0	NR	97.2	NR	152/96 (25/15); arterial: 115 (17); diastolic hypertension
ABCD-H, 2000 ⁶⁰	Moderate (DBP 80-89 mmHg)	233	57.7 (8.3)	68/32	NR	NR	100	NR	NR	31.7 (6.3)	154/98 (16.9/6.4); diastolic hypertension ≥ 90 mmHg
	Intensive (DBP 75 mmHg)	237	58.0 (8.4)	67/33	NR	NR	100	NR	NR	31.8 (5.1)	156/98 (16.1/6.4); diastolic hypertension ≥ 90 mmHg
ABCD-N, 2002 ⁶¹	Moderate (DBP 80-90 mmHg)	243	59.6 (0.5 SE)	56/44	White: 72 Black: 7 Hispanic: 18 Other: 3	Ex-smoker: 42 Current: 13	100	NR	NR	31.5 (0.4)	137.2/84.4 (0.2/0.2); normotensive
	Intensive (DBP decrease of 10 mmHg)	237	58.6 (0.6)	53/47	White: 75 Black: 7 Hispanic: 16 Other: 2	Ex-smoker: 49 Current: 13	100	NR	NR	31.5 (0.4)	135.6/84.4 (0.2/0.2); normotensive

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
CSG, 1999 ⁶²	Mean arterial pressure: ≤92 mmHg	66	37 (7)	46/54	White: 97	NR	100	NR	NR	NR	NR
	Mean arterial pressure: 100-107 mmHg	63	37 (8)	48/52	White: 92	NR	100	NR	NR	NR	NR
HOT, 1998 ⁶³	DBP ≤90 mmHg	6264	61.5 (7.5)	53/47	NR	Current: 16	8	6	52	28.4 (4.7)	170/105 (14.4/3.4); diastolic hypertension 100-115 mmHg
	DBP ≤85 mmHg	6264	61.5 (7.5)	53/47	NR	Current: 16	8	6	53	28.5 (4.7)	170/105 (14.0/3.4); diastolic hypertension 100-115 mmHg
	DBP ≤80 mmHg	6262	61.5 (7.5)	53/47	NR	Current: 16	8	6	53	28.4 (4.6)	170/105 (14.1/3.4); diastolic hypertension 100-115 mmHg
Ikeda et al, 2002 ⁶⁴	BP <130/80 mmHg	28	63 (5)	62/38	NR	NR	NR	NR	NR	NR	NR
	BP <120/75 mmHg	28			NR	NR	NR	NR	NR	NR	NR

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
MDRD, 2005 ⁶⁵	Usual (age ≤ 60 years: arterial BP <107 mmHg (<140/90 mmHg); age >60 years: arterial BP 113 mmHg)	408	52.0 (12.2)	59/41	Black: 8	NR	5	NR	NR	NR	131/80 (18/10); arterial: 97 (11)
	Low (age ≤ 60 years: arterial BP <92 mmHg (<125/75 mmHg); age >60 years: arterial BP 98 mmHg)	432	51.5 (12.6)	62/38	Black: 8	NR	5	NR	NR	NR	130/80 (16/10); arterial: 96 (10)
REIN-2, 2005 ⁶⁶	Conventional BP (DBP <90 mmHg)	168 (169 randomized; 1 never took study drugs)	53.1 (15.8)	76/24	NR	NR	NR	NR	?100	NR	136.4/83.9 (17.0/10.4)
	Intensified BP (<130/80 mmHg)	167 (169 randomized; 2 never took study drugs)	54.6 (14.7)	74/26	NR	NR	NR	NR	?100	NR	137.0/84.3 (16.7/9.0)

Study (Author, year)	Treatment arm	No. of patients	Age, years (±SD)	Male/female (%)	Race/ethnicity, %	Smoking, %	Diabetes, %	CHD, %	Prior treatment %	Mean BMI, kg/m ² (±SD)	Mean BP at baseline, SBP/DBP (±SD); type of hypertension
Toto et al, 1995 ⁶⁷	Conventional (DBP= 85-95 mmHg)	35	55.7 (1.6)	74/26	Black: 83	NR	0	NR	?100	28.2 (1.0)	122/77 (3/1); diastolic hypertension ≥ 95 mmHg
	Strict BP (DBP= 65-80 mmHg)	42	55.8 (1.5)	52/48	Black: 69	NR	0	NR	?100	28.9 (0.9)	124/76 (2/1); diastolic hypertension ≥ 95 mmHg

APPENDIX 10A: INCLUSION AND EXCLUSION CRITERIA AND MODES OF TREATMENTS OF TRIALS RELATED TO THIAZIDE DIURETICS VERSUS PLACEBO OR NO TREATMENT AND OTHER ANTIHYPERTENSIVE DRUG CLASSES

Trial, Arms (no. of patients)	Inclusion / Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years (SD)	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
Thiazide diuretics versus placebo/no treatment							
ANBP-1 ¹³ <i>CLTZ (1,721) versus Placebo (1,706)</i>	<i>Inclusion:</i> age 30 to 69 years; mild hypertension (SBP < 200 mmHg; DBP 95 -110 mmHg) <i>Exclusion:</i> on treatment for hypertension; cardiovascular events and other major diseases in the past 3 months	158 / 101	51 (9)	DBP ≤ 90; DBP: 80 after 2 years	<i>Initial:</i> CLTZ (500 mg/d or bid) <i>Step 1:</i> Methyldopa (NR); Propranolol (NR) or Pindolol (NR) <i>Step 2:</i> Hydralazine (NR) or Clonidine (NR)	Placebo	2
ANBPS ¹⁵ <i>CLTZ (293) versus Placebo (289)</i>	<i>Inclusion:</i> elderly, SBP < 200 mmHg; DBP: 95 to 110 mmHg <i>Exclusion:</i> cardiovascular events and other major diseases	156 / 101	64 (2.3)	DBP ≤ 90; DBP: 80 after 2 years	CLTZ (NR)	Placebo	1
Barracough et al ¹⁶ <i>BFTZ (58) versus Ca lactate (58)</i>	<i>Inclusion:</i> age 45 to 69 years; DBP between 100 to 120 mmHg <i>Exclusion:</i> on treatment for hypertension; cardiovascular events and other major diseases	NR / 110	55 (NR)	DBP < 100	BFTZ (NR) With potassium (NR), methyldopa (NR) or debrisoquine (NR)	Control (Ca lactate)	2
Carter ¹⁷ <i>TZD (50) versus Control (49)</i>	<i>Inclusion:</i> age ≤ 80 years; hypertensive subjects surviving ischemic-type stroke <i>Exclusion:</i> other cardiovascular and cerebrovascular diseases; tumour; kidney failure	/ > 110 or >160 / < 110	Range: 40 - 79	<160 / 90 to 100	<i>Initial:</i> TZD (NR) <i>Step1:</i> Methyldopa (≤ 1 g per day), Bethanidine or Debrisoquine (10 to 200 mg 3 to 4x per day)	Control	2
EWPHE ¹⁸ <i>HCTZ (416) versus</i>	<i>Inclusion:</i> age > 60 years; SBP: 160 to 239 mmHg, DBP 90 to 119 mmHg <i>Exclusion:</i> secondary hypertension;	183 / 101	72 (8)	NR	<i>Initial:</i> HCTZZ (25 mg, 1 to 2x per day) + Triamterene (50 mg, 1 to	Placebo	3

Trial, Arms (no. of patients)	Inclusion / Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years (SD)	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
Placebo (424)	cardiovascular events and other major diseases				2x per day) <i>Step 1:</i> Methyldopa (500 mg, 0.5 to 4 tablets per day)		
HSCSG ²⁰ <i>MCTZ (233) versus Placebo (219)</i>	<i>Inclusion:</i> stroke or transient ischemic attack survivors; SBP: 140 to 220 mmHg, DBP 90 to 115 mmHg <i>Exclusion:</i> age > 75 years; other major diseases.	167 / 100	59 (NR)	<140 / 90	1 to 2 tablets / d (5 mg MCTZ + 0.5 mg diserpidine), then 2 tablets / d	Placebo	3
HYVET ²¹ <i>BFTZ (426) versus no treatment (426)</i>	<i>Inclusion:</i> age > 80 years; hypertensive; SBP 160 to 219 mmHg, DBP 90 to 109 mmHg <i>Exclusion:</i> serum creatinine > 150 µM; cardiovascular events or other major diseases in the past 6 months	181 / 99.6	83.8	<150 / 80	<i>Initial:</i> BFTZ (2.5 mg/d) <i>Step 1:</i> double dose <i>Step 2:</i> Diltiazem SR (120 mg/d) <i>Step 3:</i> Diltiazem SR (240 mg/d)	No treatment	3
MRC-mild ²⁵ <i>BFTZ (4,297) versus Placebo (,8654)</i>	<i>Inclusion:</i> age 35 to 64 years; SBP < 200 mmHg, DBP: 90 to 109 mmHg <i>Exclusion:</i> on treatment for hypertension; cardiovascular events and other major diseases	158 / 98 (M) 165 / 99 (F)	51 (M) 53 (F)	DBP < 90	<i>Initial:</i> BFTZ (10 mg/d) <i>Step 1:</i> Methyldopa (NR)	Placebo	3
MRC-old ²⁶ <i>Coamilozide (454) versus Placebo (926)</i>	<i>Inclusion:</i> age 65 to 74 years; SBP: 160 to 209 mmHg, DBP < 115 mmHg <i>Exclusion:</i> secondary hypertension or cardiovascular events and other major diseases	183 / 92 (M) 186 / 90 (F)	70.2 (M) 70.4 (F)	SBP 150 or 160	<i>Initial:</i> 1 tablet / d (2.5 mg amiloride + 25 mg HCTZ) <i>Step 1:</i> dose doubling <i>Step 2:</i> Nifedipine (up to 20 mg/d) or other drugs	Placebo	2
OSLO ²⁸ <i>HCTZ (406) versus no treatment (379)</i>	<i>Inclusion:</i> men; age 20 to 49 years; SBP: 150 to 179 mmHg, DBP < 110 mmHg <i>Exclusion:</i> cardiovascular events or other major diseases	156 / 97	45	<140 / 90	<i>Initial:</i> HCTZZ (50 mg/d) <i>Step 1:</i> Methyldopa (250 – to 500 mg bid), propranolol (40 to 160 mg bid), or other drugs	No treatment	2
PATS ²⁹ <i>Indapamide (,2841) versus Placebo</i>	<i>Inclusion:</i> stroke or transient ischemic attack survivors; SBP 80 to 280 mmHg, DBP 50 to 150 mmHg <i>Exclusion:</i> other major diseases	154 / 93	60	NR	Indapamide (2.5 mg/d)	Placebo	4

Trial, Arms (no. of patients)	Inclusion / Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years (SD)	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
(2,824)							
PHS ³⁰ <i>CLTZ (193) versus Placebo (196)</i>	<i>Inclusion:</i> age 21 to 55 years; DBP 90 to 115 mmHg <i>Exclusion:</i> cardiovascular events or other major diseases	146 / 99	44	NR	One tablet bid (each contains 500 mg CLTZ + 100 mg rauwolfia serpentine)	Placebo	3
SHEP ³² <i>CLTD (2,365) versus Placebo (2,371)</i>	<i>Inclusion:</i> age ≥ 60 years; isolated systolic hypertension; SBP 160 to 219 mmHg, DBP < 90 mmHg <i>Exclusion:</i> cardiovascular events or other major diseases	170 / 77	71.6	SBP < 160 or reduction of at least 20	<i>Initial:</i> CLTD (12.5 mg/d) <i>Step 1:</i> dose doubling <i>Step 2:</i> Atenolol (25 mg/d) or reserpine (0.05 mg/d)	Placebo	2
SHEP-PS ³³ <i>CLTD (443) versus Placebo (108)</i>	<i>Inclusion:</i> age ≥ 60 years; isolated systolic hypertension; SBP ≥ 160 mmHg, DBP < 100 mmHg <i>Exclusion:</i> cardiovascular events or other major diseases	172 / 75	72.1	SBP < 160 or reduction of > 20	<i>Initial:</i> CLTD (25 mg/d) <i>Step 1:</i> Hydralazine, reserpine or metoprolol <i>Step 2:</i> dose doubling of step 1	Placebo	2
VA-I ³⁴ <i>HCTZZ (73) versus Placebo (70)</i>	<i>Inclusion:</i> men; DBP 115 to 129 mmHg <i>Exclusion:</i> secondary hypertension; cardiovascular events or other major diseases	186 / 121	51	DBP < 90	<i>Initial:</i> 50 mg HCTZ + 0.1 reserpine bid, and hydralazine (25 mg tid) <i>Step 1:</i> hydralazine (50 mg tid)	Placebo	4
VA-II ³⁵ <i>HCTZ (186) versus Placebo (194)</i>	<i>Inclusion:</i> men; DBP 90 to 114 mmHg <i>Exclusion:</i> secondary hypertension; cardiovascular events or other major diseases	163 / 104	51	DBP < 90	<i>Initial:</i> 50 mg HCTZ + 0.1 reserpine bid, and hydralazine (25 mg tid) <i>Step 1:</i> hydralazine (50 mg tid)	Placebo	4
VA-NHLBI ³⁶ <i>CLTD (508) versus Placebo (504)</i>	<i>Inclusion:</i> men; age 35 to 55 years; DBP 85 to 115 mmHg	DBP: 93.3	37.5	NR	<i>Initial:</i> CLTD (50 mg/d) <i>Step 1:</i> dose doubling <i>Step 2:</i> reserpine (0.25 mg/d)	Placebo	2
Thiazide diuretics versus angiotensin converting enzyme inhibitors							
ALLHAT ¹² <i>CLTD (15,255)</i>	<i>Inclusion:</i> age ≥ 55 years; stage 1 or 2 hypertension with at least one additional risk factor for CHD events	146 / 84	66.9 (7.7)	<140/90	<i>Initial:</i> CLTD (12.5, 25 mg/d)	<i>Initial:</i> Lisinopril (10, 20, 40 mg/d)	5

Trial, Arms (no. of patients)	Inclusion / Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years (SD)	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
<i>versus Lisinopril (9,054)</i>	<i>Exclusion:</i> history of hospitalized or treated symptomatic heart failure and/or known left ventricular ejection fraction of less than 35%				<i>Step 1:</i> Atenolol (25 to 100 mg/d); Reserpine (0.05 to 0.2 mg/d); Clonidine (0.1 to 0.3 mg bid) <i>Step 2:</i> Hydralazine (25 to 100 mg bid)	<i>Step 1:</i> Atenolol (25 to 100 mg/d); Reserpine (0.05 to 0.2 mg/d); Clonidine (0.1 to 0.3 mg bid) <i>Step 2:</i> Hydralazine (25 to 100 mg bid)	
ANBP-2 ¹⁴ <i>HCTZZ (3,039) versus Enalapril (3,044)</i>	<i>Inclusion:</i> elderly; SBP ≥ 160 mmHg or DBP ≥ 90 mmHg (if SBP ≥ 140 mmHg) <i>Exclusion:</i> having cardiovascular events and other major diseases in the past 6 months	168 / 91	71.9	<160/90 or <140/80	<i>Initial:</i> HCTZ (NR) Choice of dose and specific agent was made by family practitioner	<i>Initial:</i> Enalapril (NR) Choice of dose and specific agent was made by family practitioner	1
HYVET ²¹ <i>BFTZ (426) versus Lisinopril (431)</i>	<i>Inclusion:</i> age > 80 years; SBP 160 to 219 mmHg; DBP 90 to 109 mmHg <i>Exclusion:</i> serum creatinine > 150 µM; cardiovascular events and other major diseases in the past 6 months	181 / 99.6	83.8	<150 / 80	<i>Initial:</i> BFTZ (2.5 mg/d) <i>Step 1:</i> double dose <i>Step 2:</i> Diltiazem SR (120 mg/d) <i>Step 3:</i> Diltiazem SR (240 mg/d)	<i>Initial:</i> Lisinopril (2.5 mg/d) <i>Step 1:</i> double dose <i>Step 2:</i> Diltiazem SR (120 mg/d) <i>Step 3:</i> Diltiazem SR (240 mg/d)	3
Thiazide diuretics versus α-β-blockers							
HAPPY ¹⁹ <i>TZD (3,272) versus Atenolol/Metoprolol (3,297)</i>	<i>Inclusion:</i> men, age 40 to 64 years; DBP 100 to 130 mmHg <i>Exclusion:</i> previous treatment for hypertension; cardiovascular events and other major diseases	166 / 107	52.3	DBP < 95	<i>Initial:</i> BFTZ (5 mg/d) or HCTZ (50 mg/d) <i>Step 1:</i> Hydralazine (75 mg/d) <i>Step 2:</i> Hydralazine (150 mg/d) <i>Step 3:</i> Step2 + spironolactone (75 mg/d) <i>Step 4:</i> Step2 + spironolactone (150 mg/d) <i>Step 5:</i> Step 4 + Optional drug	<i>Initial:</i> Atenolol (100 mg/d), Metoprolol (200 mg/d) or propranolol (160 mg) <i>Step 1:</i> Hydralazine (75 mg/d) <i>Step 2:</i> Hydralazine (150 mg/d) <i>Step 3:</i> Step2 + spironolactone (75 mg/d) <i>Step 4:</i> Step2 + spironolactone (150 mg/d)	1

Trial, Arms (no. of patients)	Inclusion / Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years (SD)	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
						Step 5: Step 4 + Optional drug	
MAPHY ^{23,113} <i>HCTZ/BFTZ (1625) versus Metoprolol (1,609)</i>	<i>Inclusion:</i> men; age 40 to 64 years; DBP 100 to 130 mmHg <i>Exclusion:</i> secondary hypertension; cardiovascular events and other major diseases	166 / 107	52.6	DBP < 95	<i>Initial:</i> BFTZ (5 mg/d) or HCTZ (50 mg/d) <i>Step 1:</i> dose doubling <i>Step 2:</i> addition of hydralazine, spironolactone or others	<i>Initial:</i> Metoprolol (200 mg/d) <i>Step 1:</i> dose doubling <i>Step 2:</i> addition of hydralazine, spironolactone or others	1
MRC-mild ²⁵ <i>BFTZ (4,297) versus Propranolol (4,403)</i>	<i>Inclusion:</i> age 35 to 64 years; SBP < 200 mmHg; DBP 90 to 109 mmHg <i>Exclusion:</i> treatment for hypertension; cardiovascular events and other major diseases	158 / 98 (M) 165 / 99 (F)	51 (M) 53 (F)	DBP < 90	<i>Initial:</i> BFTZ (10 mg/d) <i>Step 1:</i> Methyldopa (NR)	<i>Initial:</i> Propranolol (up to 240 mg/d) <i>Step 1:</i> Guanethidine (NR)	3
MRC-old ²⁶ <i>Coamilozide (454) versus Atenolol (456)</i>	<i>Inclusion:</i> age 65 to 74 years; SBP 160 to 209 mmHg; DBP < 115 mmHg <i>Exclusion:</i> secondary hypertension; cardiovascular events and other major diseases	183 / 92 (M) 186 / 90 (F)	70.2 (M) 70.4 (F)	SBP 150 or 160	<i>Initial:</i> 1 tablet / d (2.5 mg amiloride + 25 mg HCTZ) <i>Step 1:</i> dose doubling <i>Step 2:</i> Nifedipine (up to 20 mg/d) or other drugs	<i>Initial:</i> Atenolol (50 mg/d) <i>Step 1:</i> dose doubling <i>Step 2:</i> Nifedipine (up to 20 mg/d) or other drugs	2
Thiazide diuretics versus calcium channel blockers							
ALLHAT ¹² <i>CLTD (15,255) versus Amlodipine (9,048)</i>	<i>Inclusion:</i> age ≥ 55 years; stage 1 or 2 hypertension with at least one additional risk factor for CHD events <i>Exclusion:</i> history of hospitalized or treated symptomatic heart failure and/or known left ventricular ejection fraction of less than 35%	146 / 84	66.9 (7.7)	<140/90	<i>Initial:</i> CLTD (12.5, 25 mg/d) <i>Step 12:</i> Atenolol (25 to 100 mg/d); Reserpine (0.05 to 0.2 mg/d); Clonidine (0.1 to 0.3 mg bid) <i>Step 2:</i> Hydralazine (25 to 100 mg bid)	<i>Initial:</i> Amlodipine (2.5, 5, 10 mg/d) <i>Step 1:</i> Atenolol (25 to 100 mg/d); Reserpine (0.05 to 0.2 mg/d); Clonidine (0.1 to 0.3 mg bid) <i>Step 2:</i> Hydralazine (25 to 100 mg bid)	5
INSIGHT ²² <i>Coamilozide (3,286) versus Nifedipine (3,289)</i>	<i>Inclusion:</i> age 55 to 80 years; hypertension (> 150/95 mmHg); at least one additional cardiovascular risk factor	173 / 99	65	<140/90	<i>Initial:</i> Co-amilozide (25 mg/d HCTZ + 2.5 mg/d amiloride) <i>Step 1:</i> dose doubling	<i>Initial:</i> Nifedipine (30 mg/d) <i>Step 1:</i> dose doubling <i>Step 2:</i> Atenolol (25	2

Trial, Arms (no. of patients)	Inclusion / Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years (SD)	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
					<i>Step 2:</i> Atenolol (25 mg/d) or Enalapril (5 mg/d) <i>Step 3:</i> dose doubling of step 2 <i>Step 4:</i> addition of other antihypertensive drugs	mg/d) or Enalapril (5 mg/d) <i>Step 3:</i> dose doubling of step 2 <i>Step 4:</i> addition of other antihypertensive drugs	
MIDAS ²⁴ <i>HCTZ (441) versus Isradipine (442)</i>	<i>Inclusion:</i> age $\geq$ 40 years; DBP 90 to 115 mmHg <i>Exclusion:</i> hyperlipidemia; cardiovascular events or other major diseases	150 / 97	58.5	DBP < 90 or 95	<i>Initial:</i> HCTZ (12.5 to 25 mg bid) <i>Step 1 – 4:</i> Enalapril (2.5, 5.0, 7.5 or 10 mg/d)	<i>Initial:</i> Isradipine (2.5 to 5.0 mg bid) <i>Step 1 – 4:</i> Enalapril (2.5, 5.0, 7.5 or 10 mg/d)	2
NICS-EH ²⁷ <i>TMTZ (210) versus Nicardipine (204)</i>	<i>Inclusion:</i> age $\geq$ 60 years; SBP 160 to 220 mmHg; DBP < 115 mmHg <i>Exclusion:</i> secondary hypertension or cardiovascular complications	172 / 94	69.8	NR	TMTZ (2 mg/d)	Nicardipine SR (20 mg bid)	2
SHELL ³¹ <i>CLTD (940) versus Lacidipine (942)</i>	<i>Inclusion:</i> age $\geq$ 60 years;; SBP $\geq$ 160 mmHg, DBP $\leq$ 95 mmHg <i>Exclusion:</i> secondary hypertension or cardiovascular events within the previous 6 months	178 / 87	72	SBP < 160	<i>Initial:</i> CLTD (12.5 mg/d) <i>Step 1:</i> CLTD (12.5 mg/d) <i>Step 2:</i> CLTD (12.5 mg/d) + fosinopril (10 mg/d) or other ACEI	<i>Initial:</i> Lacidipine (4 mg/d) <i>Step 1:</i> Lacidipine (6 mg/d) <i>Step 2:</i> Lacidipine (4 mg/d) + fosinopril (10 mg/d) or other ACEI	1
VHAS ³⁸ <i>CLTD (707) versus Verapamil (707)</i>	<i>Inclusion:</i> age 40 to 65 years; SBP $\geq$ 160 mmHg; DBP $\geq$ 95 mmHg <i>Exclusion:</i> secondary hypertension or cardiovascular events within the previous 6 months	169 / 102	54.5	DBP $\leq$ 90 or 95	<i>Initial:</i> CLTD (25 mg/d) <i>Step 1:</i> Captopril (25 mg/d) <i>Step 2:</i> Captopril (25 mg bid)	<i>Initial:</i> Verapamil SR (240 mg/d) <i>Step 1:</i> Captopril (25 mg/d) <i>Step 2:</i> Captopril (25 mg bid)	3

a: mean $\pm$ SD; b: mean $\pm$ SE; CV: cardiovascular events; CHD: coronary heart disease events; MI: myocardial infarction events; HF: heart failure events; CRV: cerebrovascular events; RF: renal failure; NR: not reported; DM: diabetes mellitus; NR: not reported

TZD: thiazide/diuretics; BB: β -blockers; AB: α -blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; HCTZ: hydrochlorothiazide; BFTZ: bendroflumethiazide or bendrofluazide; TMTZ: trichlomethiazide; CLTZ: chlorothiazide; MCTZ: methyclothiazide; C: comparators; CLTD: chlorthalidone

APPENDIX 10B: INCLUSION AND EXCLUSION CRITERIA AND MODES OF TREATMENTS OF TRIALS RELATED TO QOL

Trial	Inclusion and Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
1. Thiazide diuretics versus placebo/no treatment							
Bird et al ⁴⁰	<i>Inclusion:</i> age 65 to 74 years;; SBP 160 to 209 mmHg, DBP ≤ 113 mmHg <i>Exclusion:</i> NR	184 / 90	70 (range: 65 to 74)	<150 or <160	<i>Initial:</i> Moduretic (25 mg/d HCTZ, 2.5 mg/d amiloride) <i>Step 1:</i> dose doubling or additional drugs	Placebo Those not attained target BP after 6 months, switched to moduretic or atenolol	1
Chang et al ⁴²	<i>Inclusion:</i> age 35 to 70 years; SBP >140 mmHg; DBP 90 to 105 mmHg <i>Exclusion:</i> taking antihypertensive medication other than diuretic; cardiovascular events and other major diseases	142 / 85	60 to 61	NR	Randomized to 1 of 5 thiazide diuretic treatment groups	Placebo	4
EWPHE ¹⁸	<i>Inclusion:</i> age > 60 years; SBP 160 to 239 mmHg; DBP 90 to 119 mmHg <i>Exclusion:</i> secondary hypertension; cardiovascular events and other major diseases	183 / 101	72 (8)	NR	<i>Initial:</i> HCTZZ (25 mg 1 to 2x per day) + Triamterene (50 mg 1 to 2x per day) <i>Step 1:</i> Methyldopa (500 mg 0.5 to 4 tablets per day)	Placebo	3
MRC-mild ²⁵	<i>Inclusion:</i> age 35 to 64 years; SBP < 200 mmHg; DBP 90 to 109 mmHg <i>Exclusion:</i> treatment for hypertension; cardiovascular events and other major diseases	158 / 98 (M) 165 / 99 (F)	51 (M) 53 (F)	DBP < 90	<i>Initial:</i> BFTZ (10 mg/d) <i>Step 1:</i> Methyldopa (NR)	Placebo	3
SHEP ³²	<i>Inclusion:</i> age ≥ 60 years; isolated systolic hypertension, SBP 160 to 219 mmHg, DBP < 90 mmHg <i>Exclusion:</i> cardiovascular events or other major diseases	170 / 77	71.6	SBP < 160 or reduction of at least 20	<i>Initial:</i> CLTD (12.5 mg/d) <i>Step 1:</i> dose doubling <i>Step 2:</i> Atenolol (25 mg/d) or reserpine (0.05	Placebo	2

Trial	Inclusion and Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
					mg/d)		
TOHMS ^{56,116,117}	<i>Inclusion:</i> age 45 to 69 years; DBP 90 to 99 mmHg; taking one type of antihypertensive drugs (DBP < 95 mmHg), and responding to initial treatment (DBP < 95 mmHg) <i>Exclusion:</i> using more than one type of antihypertensive drugs, abnormal and unwilling to change life style, cardiovascular events or other major diseases	>140 / >90	54.8	DBP < 95	<i>Initial:</i> CLTD (15 mg/d) <i>Step 1:</i> dose doubling	Placebo	3
VA-II ³⁵	<i>Inclusion:</i> men; DBP 90 to 114 mmHg <i>Exclusion:</i> secondary hypertension; cardiovascular events or other major diseases	163 / 104	51	DBP < 90	<i>Initial:</i> 50 mg HCTZ + 0.1 reserpine bid, and hydralazine (25 mg tid) <i>Step 1:</i> hydralazine (50 mg tid)	Placebo	4
VA-NHLBI ³⁶	<i>Inclusion:</i> men; age 35 to 55 years; DBP 85 to 115 mmHg	DBP: 93.3	37.5	NR	<i>Initial:</i> CLTD (50 mg/d) <i>Step 1:</i> dose doubling <i>Step 2:</i> reserpine (0.25 mg/d)	Placebo	2
Wassertheil-Smoller et al ⁵⁸	<i>Inclusion:</i> age 21 to 65 years; DBP 90 to 100 mmHg <i>Exclusion:</i> cardiovascular events or other major diseases; pregnancy	DBP: 90 – 100	49	NR	CLTD (NR)	Placebo	1
2. Thiazide diuretics versus angiotensin converting enzyme inhibitors							
Boissel et al ⁴¹	<i>Inclusion:</i> age >18 years; DBP 90 to 119 mmHg; no previous antihypertensive treatment	166 / 100	51	NR	Altizide or spironolactone (15 – 25 mg/d)	Enalapril (20 mg/d)	2
Glick et al ⁴⁴	<i>Inclusion:</i> age 30 to 65+ years; SBP < 180 mmHg; DBP < 120 mmHg <i>Exclusion:</i> renal disease or cardiovascular events	<180 / <120	NR	NR	HCTZ-triamterene (NR)	Captopril (25 mg/d)	1
Lacourciere et al ⁴⁵	<i>Inclusion:</i> age 25 to 68 years; DBP 92 to 114 mmHg	DBP: 92 - 114	50	NR	Indapamide (2.5 mg/d)	Captopril (12.5 to 50 mg bid)	2

Trial	Inclusion and Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
	<i>Exclusion:</i> secondary hypertension						
Malmqvist et al ⁴⁶	<i>Inclusion:</i> women; age 40 to 69 years; DBP 95 to 115 mmHg <i>Exclusion:</i> secondary hypertension; SBP > 200 mmHg, cardiovascular or other chronic diseases	NR	57.7	DBP <90	<i>Initial:</i> HCTZ (12.5 mg/d) <i>Step 1:</i> dose doubling	<i>Initial:</i> Enalapril (10 mg/d) <i>Step 1:</i> dose doubling	4
Martin et al ⁴⁷	<i>Inclusion:</i> age 21 to 65 years; DBP 95 to 120 mmHg <i>Exclusion:</i> other chronic diseases	169 / 103	NR	normotensive	HCTZ (25 to 50 mg/d)	Captopril (50 to 150 mg/d)	2
Metelitsa et al ⁴⁸	<i>Inclusion:</i> men; age 30 to 60 years; DBP 95 to 114 mmHg <i>Exclusion:</i> other chronic diseases	NR	NR	NR	HCTZ (25 or 50 mg/d)	Captopril (50 mg od and 50 mg bid)	1
Starr et al ⁵³	<i>Inclusion:</i> age 70 to 85 years; SBP 160 to 220 mmHg; DBP 100 to 120 mmHg	191 / 101	76.1	DBP decreased by 10%	<i>Initial:</i> BFTZ (2.5 mg /d) <i>Step 1:</i> dose doubling	<i>Initial:</i> Captopril (12.5 mg bid) <i>Step 1:</i> dose doubling	2
Suzuki et al ⁵⁴	<i>Inclusion:</i> men; age 22 to 55 years; DBP 95 to 110 mmHg	DBP: 95 to 100	NR	DBP < 90	TMTZ: 2 to 4 mg/d	Captopril: 37.5 to 50 mg/d	1
TOHMS ^{56,116,117}	<i>Inclusion:</i> age 45 to 69 years; DBP 90 to 99 mmHg; or taking one type of antihypertensive drug (DBP < 95 mmHg), and responding to initial treatment (DBP < 95 mmHg) <i>Exclusion:</i> using more than one type of antihypertensive drug; abnormal and unwilling to change life style; cardiovascular events or other major diseases	>140 / >90	54.8	DBP < 95	<i>Initial:</i> CLTD (15 mg/d) <i>Step 1:</i> dose doubling	<i>Initial:</i> Enalapril (5 mg/d) <i>Step 1:</i> dose doubling	3
3. Thiazide diuretics versus α- or β-blockers							
Bird et al ⁴⁰	<i>Inclusion:</i> age 65 to 74 years; SBP 160 to 209 mmHg; DBP $\leq$ 113 mmHg <i>Exclusion:</i> NR	184 / 90	70 (range: 65- to 74)	<150 or <160	<i>Initial:</i> Moduretic (25 mg/d HCTZ, 2.5 mg/d amiloride) <i>Step 1:</i> dose doubling or additional drugs	<i>Initial:</i> Atenolol (50 mg/d) <i>Step 1:</i> dose doubling or additional drugs	1
Boissel et al ⁴¹	<i>Inclusion:</i> age >18 years; DBP 90 to 119	166 / 100	51	NR	Altizide or	Bisoprolol (10 mg/d)	2

Trial	Inclusion and Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
	mmHg; no previous antihypertensive treatment				spironolactone (15 to 25 mg/d)		
Glick et al ⁴⁴	<i>Inclusion:</i> age 30 to 65+ years; SBP < 180 mmHg; DBP < 120 mmHg <i>Exclusion:</i> renal disease or cardiovascular events	<180 / <120	NR	NR	HCTZ-triamterene (NR)	Metoprolol (100 mg/d)	1
HAPPHY ¹⁹	<i>Inclusion:</i> men; age 40 to 64 years; DBP 100 to 130 mmHg <i>Exclusion:</i> previous treatment for hypertension; cardiovascular events and other major diseases	166 / 107	52.3	DBP < 95	<i>Initial:</i> BFTZ (5 mg/d) or HCTZ (50 mg/d) <i>Step 1:</i> Hydralazine (75 mg/d) <i>Step 2:</i> Hydralazine (150 mg/d) <i>Step 3:</i> Step2 + spironolactone (75 mg/d) <i>Step 4:</i> Step2 + spironolactone (150 mg/d) <i>Step 5:</i> Step 4 + Optional drug	<i>Initial:</i> Atenolol (100 mg/d), Metoprolol (200 mg/d) or propranolol (160 mg) <i>Step 1:</i> Hydralazine (75 mg/d) <i>Step 2:</i> Hydralazine (150 mg/d) <i>Step 3:</i> Step2 + spironolactone (75 mg/d) <i>Step 4:</i> Step2 + spironolactone (150 mg/d) <i>Step 5:</i> Step 4 + Optional drug	1
Metelitsa et al ⁴⁸	<i>Inclusion:</i> men; age 30 to 60 years; DBP 95 to 114 mmHg <i>Exclusion:</i> other chronic diseases	NR	NR	NR	HCTZZ (25 or 50 mg/d)	Propranolol (40 and 120 mg bid)	1
MRC-mild ⁴⁹	<i>Inclusion:</i> age 35 to 64 years; SBP < 200 mmHg; DBP 90 to 109 mmHg <i>Exclusion:</i> on treatment for hypertension; cardiovascular events and other major diseases	158 / 98 (M) 165 / 99 (F)	51 (M) 53 (F)	DBP < 90	<i>Initial:</i> BFTZ (10 mg/d) <i>Step 1:</i> Methyldopa (NR)	<i>Initial:</i> Propranolol (up to 240 mg/d) <i>Step 1:</i> Guanethidine (NR)	3
Potempa et al ⁵¹	<i>Inclusion:</i> age 28 to 75 years; primary hypertension <i>Exclusion:</i> secondary hypertension;	148 / 100	51	DBP < 95	<i>Initial:</i> HCTZ (33 mg/d) <i>Step 1:</i> HCTZ (100 mg/d)	<i>Initial:</i> Propranolol (160 mg/d), pindolol (20 mg/d)	1

Trial	Inclusion and Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
	cardiovascular events or other major diseases; pregnancy					<i>Step 1:</i> Propranolol (480 mg/d), pindolol (60 mg/d)	
Slovick et al ⁵² 24 weeks	<i>Inclusion:</i> age 65 to 90 years; SBP $\geq$ 160 mmHg; DBP 90 to 114 mmHg <i>Exclusion:</i> other major diseases	182 / 100	72	DBP < 90	BFTZ (2.5 to 5 mg/d)	Dilevalol (200 to 400 mg/d)	2
Suzuki et al ⁵⁴	<i>Inclusion:</i> men; age 22 to 55 years; DBP 95 to 110 mmHg	DBP: 95 to 100	NR	DBP < 90	TMTZ: 2 to 4 mg/d	Atenolol: 50 to 100 mg/d	1
TOHMS ^{56,116,117}	<i>Inclusion:</i> age 45 to 69 years; DBP 90 to 99 mmHg; taking one type of antihypertensive drug (DBP < 95 mmHg), and responding to initial treatment (DBP < 95 mmHg) <i>Exclusion:</i> using more than one type of antihypertensive drug; abnormal and unwilling to change life style; cardiovascular events or other major diseases	>140 / >90	54.8	DBP < 95	<i>Initial:</i> CLTD (15 mg/d) <i>Step 1:</i> dose doubling	<i>Initial:</i> Acebutolol (400 mg/d) or Doxazosin (1 mg/d) <i>Step 1:</i> dose doubling	3
Vanmolkot et al ⁵⁷	<i>Inclusion:</i> hypertension, DBP 95 to 120 mmHg <i>Exclusion:</i> cardiovascular events; pregnancy; intolerance to thiazides or β -blockers; other major diseases	160 / 103	61	DBP < 95	<i>Initial:</i> BFTZ (2.5 mg/d) <i>Step 1:</i> dose doubling	<i>Initial:</i> Bisoprolol (5 mg/d) <i>Step 1:</i> dose doubling	3
Wassertheil-Smoller et al ⁵⁸	<i>Inclusion:</i> age 21 to 65 years; DBP 90 to 100 mmHg <i>Exclusion:</i> cardiovascular events or other major diseases; pregnancy	DBP: 90 - 100	49	NR	CLTD (NR)	Atenolol (NR)	1
4. Thiazide diuretics versus calcium channel blockers							
Boissel et al ⁴¹	<i>Inclusion:</i> age >18 years; DBP 90 to 119 mmHg; no previous antihypertensive treatment <i>Exclusion:</i> ?	166 / 100	51	NR	Altizide or spironolactone (15 to 25 mg/d)	Verapamil (240 mg/d)	2
Metelitsa et al ⁴⁸	<i>Inclusion:</i> men; age 30 to 60 years; DBP 95 to 114 mmHg <i>Exclusion:</i> other chronic diseases	NR	NR	NR	HCTZ (25 or 50 mg/d)	Nifedipine (20 and 30 mg tid)	1

Trial	Inclusion and Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
Ogihara et al (NICS-EH) ⁵⁰	<i>Inclusion:</i> age ≥ 60 years; SBP 160 to 220 mmHg; DBP < 115 mmHg <i>Exclusion:</i> secondary hypertension or cardiovascular complications	172 / 94	69.8	NR	TMTZ (2 mg/d)	Nicardipine SR (20 mg bid)	2
SHELL ³¹	<i>Inclusion:</i> age ≥ 60 years; SBP ≥ 160 mmHg; DBP ≤ 95 mmHg <i>Exclusion:</i> secondary hypertension or cardiovascular events within the previous 6 months	178 / 87	72	SBP < 160	<i>Initial:</i> CLTD (12.5 mg/d) <i>Step 1:</i> CLTD (12.5 mg/d) <i>Step 2:</i> CLTD (12.5 mg/d) + fosinopril (10 mg/d) or other ACEI	<i>Initial:</i> Lacidipine (4 mg/d) <i>Step 1:</i> Lacidipine (6 mg/d) <i>Step 2:</i> Lacidipine (4 mg/d) + fosinopril (10 mg/d) or other ACEI	1
Suzuki et al ⁵⁴	<i>Inclusion:</i> men; age 22 to 55 years; DBP 95 to 110 mmHg	DBP: 95 - 100	NR	DBP < 90	TMTZ: 2 to 4 mg/d	Nifedipine SR: 40 to 80 mg/d	1
TOHMS ^{56,116,117}	<i>Inclusion:</i> 45 to 69 years; DBP 90 to 99 mmHg, or taking one type of antihypertensive drug (DBP < 95 mmHg), and responding to initial treatment (DBP < 95 mmHg) <i>Exclusion:</i> using more than one type of antihypertensive drug; abnormal and unwilling to change life style; cardiovascular events or other major diseases	$> 140 / > 90$	54.8	DBP < 95	<i>Initial:</i> CLTD (15 mg/d) <i>Step 1:</i> dose doubling	<i>Initial:</i> Amlodipine (5 mg/d) <i>Step 1:</i> dose doubling	3
VHAS ³⁸	<i>Inclusion:</i> age 40 to 65 years; hypertension; SBP ≥ 160 mmHg; DBP ≥ 95 mmHg <i>Exclusion:</i> secondary hypertension or cardiovascular events within the previous 6 months	169 / 102	54.5	DBP ≤ 90 or 95	<i>Initial:</i> CLTD (25 mg/d) <i>Step 1:</i> Captopril (25 mg/d) <i>Step 2:</i> Captopril (25 mg bid)	<i>Initial:</i> Verapamil SR (240 mg/d) <i>Step 1:</i> Captopril (25 mg/d) <i>Step 2:</i> Captopril (25 mg bid)	3
5. Thiazide diuretics versus angiotensin receptor blockers							
ALPINE ³⁹	<i>Inclusion:</i> hypertension; SBP 140 to 179 mmHg; DBP 90 to 104 mmHg <i>Exclusion:</i> other chronic diseases	155 / 97	55	$< 130 / 85$ or $< 140 / 90$	<i>Initial:</i> HCTZ (25 mg/d) <i>Step 1:</i> Atenolol (50 to 100 mg/d)	<i>Initial:</i> Candesartan (16 mg/d) <i>Step 1:</i> Felodipine (2.5 to 5 mg/d)	3
Malmqvist et al ⁴⁶	<i>Inclusion:</i> women; age 40 to 69 years; DBP	NR	57.7	DBP < 90	<i>Initial:</i> HCTZZ (12.5	<i>Initial:</i> Candesartan (8	4

Trial	Inclusion and Exclusion criteria	Mean SBP/DBP at baseline, mmHg	Mean age, years	Goal BP, mmHg	Treatment (dosage)		Jadad score
					Thiazide diuretics	Comparators	
	95 to 115 mmHg <i>Exclusion:</i> secondary hypertension; SBP > 200 mmHg; cardiovascular or other chronic diseases				mg/d) <i>Step 1:</i> dose doubling	mg/d) <i>Step 1:</i> dose doubling	
Tedesco et al ⁵⁵	<i>Inclusion:</i> age 30 to 73 years; DBP 90 to 114 mmHg <i>Exclusion:</i> other chronic diseases	151 / 94	NR	NR	HCTZ (25 mg/d)	Losartan (50 mg/d)	2

a: mean $\pm$ SD; b: mean $\pm$ SE; CV: cardiovascular events; CHD: coronary heart disease events; MI: myocardial infarction events; HF: heart failure events; CRV: cerebrovascular events; RF: renal failure; NR: not reported; DM: diabetes mellitus; NR: not reported; TZD: thiazide/diuretics; BB: β -blockers; AB: α -blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; HCTZ: hydrochlorothiazide; BFTZ: bendroflumethiazide or bendrofluazide; TMTZ: trichlomethiazide; CLTZ: chlorothiazide; MCTZ: methyclothiazide; C: comparators; CLTD: chlorthalidone

APPENDIX 10C: INCLUSION AND EXCLUSION CRITERIA AND MODES OF TREATMENTS OF TRIALS RELATED TO BP TARGET

Trial	Inclusion and Exclusion criteria	BP goal, mm Hg		Treatment (dosage)	Jadad score
		Moderate	Intense		
AASK ^{59,68}	<i>Inclusion:</i> African Americans, hypertensive, age 18 to 70 years, GFR 20 to 65 ml/min/1.73 m². <i>Exclusion:</i> DBP <95 mmHg, secondary hypertension, diabetes mellitus, urinary protein to creatinine ratio > 2.5, other major diseases.	MAP 102 to 107	MAP ≤ 92	<i>Initial:</i> 1 of 3 antihypertensive drugs: metoprolol (50 to 200 mg/d), ramipril (2.5 to 10 mg/d) or amlodipine (5 to 10 mg/d) <i>Stepwise:</i> furosimide, doxazosin, clonidine, and hydralazine or minoxidil added sequentially until reaching BP goal	3
ABCD-H ⁶⁰	<i>Inclusion:</i> type 2 diabetes, age 40 to 74 years, DBP ≥ 90 mmHg, previously treated for hypertension <i>Exclusion:</i> allergy to dihydropyridines or ACE inhibitors, cardiovascular events within previous 3 to 6 months or serum creatinine > 3 mg/dl	DBP 80 to 89	DBP 75	<i>Initial:</i> 1 of 2 antihypertensive drugs: nisoldipine (10 to 60 mg/d) or enalapril (5 to 40 mg/d) <i>Stepwise:</i> metoprolol and HCTZ added sequentially until reaching BP goal	1
ABCD-N ⁶¹	<i>Inclusion:</i> type 2 diabetes, age 40 to 74 years, DBP 80 to 98 mmHg, no previous treatment for hypertension <i>Exclusion:</i> allergy to dihydropyridines or ACE inhibitors, cardiovascular events within previous 6 months or serum creatinine > 3 mg/dl	DBP: 80 to 89	DBP: 70 to 78	<i>Initial:</i> 1 of 2 antihypertensive drugs: nisoldipine (10 to 60 mg/d) or enalapril (5 to 40 mg/d) <i>Stepwise:</i> metoprolol and HCTZ added sequentially until reaching BP goal. Other antihypertensive drugs were used as needed, but no CCB or ACE inhibitors	1
CSG ⁶²	<i>Inclusion:</i> type 1 diabetes for ≥ 7 years, age 18 to 40 years, onset before age 30, diabetic nephropathy, urinary protein excretion of ≥ 500 mg/24 h, serum creatinine ≤ 2.5 mg/dl <i>Exclusion:</i> serum creatinine > 4 mg/dl, potassium ≥ 6 mEq/L, cardiovascular events or other major diseases	MAP 100 to 107	MAP ≤ 92	<i>Initial:</i> Ramipril (1.25, 2.5 mg/d) <i>Stepwise:</i> Ramipril (2.5, 5, 10 mg/d). other antihypertensive drugs were used as needed, but no ACE inhibitors or ARB	2

HOT ^{63,114}	<i>Inclusion:</i> age 50 to 80 years, hypertension, mean DBP 105 mmHg <i>Exclusion:</i> NR	DBP ≤ 90	DBP ≤ 80	<i>Initial:</i> Felodipine (5 mg/d) <i>Step 1:</i> ACE inhibitors or β-blockers <i>Step 2:</i> Felodipine (10 mg/d) <i>Step 3:</i> dose doubling of step 2	5
Ikeda et al ⁶⁴	<i>Inclusion:</i> heart failure and renal dysfunction, age 44 to 84 years, serum creatinine > 1.4 mg/dl or creatinine clearance < 50 ml/min <i>Exclusion:</i> NR	SBP/DBP: <130/80	SBP/DBP: <120/75	<i>Initial:</i> Amlodipine (5 mg/d) and benazepril (2.5 or 5 mg/d) <i>Step 1:</i> Amlodipine (up to 20 mg/d) <i>Step 2:</i> Furosemide (up to 60 mg/d) <i>Step 3:</i> Guanabenz (2 to 8 mg/d)	1
MDRD ⁶⁵	<i>Inclusion:</i> chronic kidney disease, age 18 to 70 years <i>Exclusion:</i> had diabetes, kidney transplant or other major diseases.	SBP/DBP <140/90 MAP 107	SBP/DBP <125/75 MAP 92	Usual or low protein diet Antihypertensive drugs: ACE inhibitors, BB, CCB, diuretics or other.	2
REIN-2 ⁶⁶	<i>Inclusion:</i> non-diabetic nephropathy and persistent proteinuria, age 18 to 70 years <i>Exclusion:</i> treatment with corticosteroids or NSAID, cardiovascular or other major diseases	DBP < 90	SBP/DBP <130/80	Low-sodium diet and protein intake of about 0.8 g/kg/d Antihypertensive drugs: ACE inhibitors, ARB, dihydropyridine CCB	2
Toto et al ⁶⁷	<i>Inclusion:</i> hypertensive nephrosclerotic patients, age 25 to 73 years, DBP ≥ 95 mmHg, serum creatinine > 1.6 mg/dl, GFR ≤ 70 ml/min/1.73 m ² <i>Exclusion:</i> diabetes, cardiovascular events or other major diseases	DBP 85 to 95	DBP 65 to 80	<i>First 6 months:</i> Step-care approach (Step 1: diuretic, Step 2: β-blockers, Step 3: hydralazine or monoxidil, Step 4: clonidine, α-methyldopa or α ₁ -blocker) to lower DBP to ≤ 80 mmHg <i>Randomization:</i> either placebo or ramipril to either BP goals	2

a: mean ± SD; b: mean ± SE; SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); GFR: glomerular filtration rate (ml/min/1.73 m²); NS: not statistically significant between treatments; CC: creatinine clearance (ml/min/1.73 m²); MI: myocardial infarction events; CHD: coronary heart disease events; CRV: cerebrovascular events; MAP: mean arterial pressure (mmHg); CV: cardiovascular events; RF: renal failure events; NR: not reported

APPENDIX 11A: QUALITY ASSESSMENT OF RCTS RELATED TO THIAZIDE DIURETICS VERSUS PLACEBO OR NO TREATMENT AND OTHER ANTIHYPERTENSIVE DRUG CLASSES

Trial	Score on Jadad scale			Total score on Jadad scale	Allocation concealment	Blinding of outcome assessor	Analyses: Intent-to- treat
	Rando- mization	Double blinding	Withdrawals and dropouts				
ALLHAT ¹²	2	2	1	5	Unclear	Yes	Yes
ANBP-1 ¹³	1	0	1	2	Unclear	NR	Yes
ANBP-2 ¹⁴	1	0	0	1	Unclear	NR	Yes
ANBPS ¹⁵	1	0	0	1	Unclear	NR	NR
Barracough et al ¹⁶	1	0	1	2	Unclear	No	NR
Carter et al ¹⁷	1	0	1	2	Unclear	NR	NR
EWPH ¹⁸	1	2	0	3	Unclear	NR	Yes
HAPPY ¹⁹	1	0	0	1	Unclear	NR	Yes
HSCSG ²⁰	1	1	1	3	Unclear	NR	NR
HYVET ²¹	2	1	0	3	Unclear	NR	Yes
INSIGHT ²²	0	1	1	2	Unclear	NR	Yes
MAPHY ^{23,113}	1	0	0	1	Unclear	NR	NR
MIDAS ²⁴	1	1	0	2	Unclear	NR	NR
MRC – Mild ²⁵	1	1	1	3	Unclear	NR	Yes
MRC – Old ²⁶	1	0	1	2	Unclear	NR	Yes
NICS – EH ²⁷	1	1	0	2	Unclear	NR	NR
OSLO ²⁸	2	0	0	2	Unclear	NR	NR
PATS ²⁹	2	1	1	4	Unclear	NR	Yes
PHS ³⁰	1	1	1	3	Unclear	NR	NR
SHELL ³¹	1	0	0	1	Unclear	NR	NR
SHEP ³²	1	1	0	2	Unclear	NR	Yes
SHEP – PS ³³	1	1	0	2	Unclear	NR	NR
VA-I ³⁴	2	2	0	4	Unclear	NR	NR
VA-II ³⁵	1	2	1	4	Unclear	NR	NR
VA-NHLBI ³⁶	1	1	0	2	Unclear	NR	NR
VHAS ³⁸	1	1	1	3	Unclear	NR	Yes

NR, not reported

APPENDIX 11B: QUALITY ASSESSMENT OF RCTS RELATED TO QOL

Trial	Score on Jadad scale			Total score on Jadad scale	Allocation concealment	Blinding of outcome assessor	Analyses: Intent-to-treat
	Rando-mization	Double blinding	Withdrawals and dropouts				
ALPINE ³⁹	1	1	1	3	Unclear	NR	Yes
Bird et al ⁴⁰	1	0	0	1	Unclear	NR	NR
Boissel et al ⁴¹	1	0	1	2	Unclear	NR	NR
Chang et al ⁴²	2	1	1	4	Unclear	Yes	NR
EWPHE ⁴³	1	2	0	3	Unclear	NR	Yes
Glick et al ⁴⁴	1	0	0	1	Unclear	NR	NR
HAPPY ¹⁹	1	0	0	1	Unclear	NR	Yes
Lacourciere et al ⁴⁵	1	0	1	2	Unclear	NR	NR
Malmqvist et al ⁴⁶	1	2	1	4	Unclear	NR	Yes
Martin et al ⁴⁷	1	0	1	2	Unclear	NR	NR
Metelitsa et al ⁴⁸	1	0	0	1	Unclear	NR	NR
MRC-mild ⁴⁹	1	1	1	3	Unclear	NR	Yes
Ogihara et al ⁵⁰	1	1	0	2	Unclear	NR	NR
Potempa et al ⁵¹	1	0	0	1	Unclear	NR	NR
SHELL ³¹	1	0	0	1	Unclear	NR	NR
SHEP ³²	1	1	1	3	Unclear	NR	Yes
Slovick et al ⁵²	1	1	0	2	Adequate	NR	NR
Starr et al ⁵³	1	1	0	2	Unclear	NR	Yes
Suzuki et al ⁵⁴	1	0	0	1	Unclear	NR	NR
Tedesco et al ⁵⁵	1	1	0	2	Unclear	NR	NR
TOMHS ^{56,116,117}	1	1	1	3	Unclear	NR	Yes
VA-II ³⁵	1	2	1	4	Unclear	NR	NR
VA-NHLBI ³⁶	1	1	0	2	Unclear	NR	NR
Vanmolkot et al ⁵⁷	1	1	1	3	Unclear	NR	Yes
VHAS ³⁷	1	1	1	3	Unclear	NR	Yes
Wassertheil-Smoller et al ⁵⁸	1	0	0	1	Unclear	NR	NR

NR, not reported

APPENDIX 11C: QUALITY ASSESSMENT OF RCTS RELATED TO BP TARGET

Trial	Score on Jadad scale			Total score on Jadad scale	Allocation concealment	Blinding of outcome assessor	Analyses: Intent-to-treat
	Rando-mization	Double blinding	Withdrawals and dropouts				
AASK ^{59,68}	1	1	1	3	Unclear	NR	Yes
ABCD-H ⁶⁰	1	0	0	1	Unclear	No	NR
ABCD-N ⁶¹	1	0	0	1	Unclear	NR	NR
CSG ⁶²	1	0	1	2	Unclear	NR	Yes
HOT ^{63,114}	2	2	1	5	Unclear	Yes	NR
Ikeda et al ⁶⁴	1	0	0	1	Unclear	NR	NR
MDRD ⁶⁵	1	0	1	2	Unclear	NR	Yes
REIN-2 ⁶⁶	1	0	1	2	Unclear	NR	Yes
Toto et al ⁶⁷	1	1	0	2	Unclear	NR	Yes

NR, not reported

APPENDIX 12: CLINICAL OUTCOMES FROM TRIALS RELATED TO THIAZIDE DIURETICS VERSUS PLACEBO/NO TREATMENT AND OTHER ANTIHYPERTENSIVE DRUG CLASSES

Trial <i>Intervention (N) vs Comparator (N)</i>	All CV		CHD		MI		HF		Stroke		CRV		RF		CV death		All death		Withdraw due to AE		SBP/DBP	
	events														n						mmHg (SD)	
	TZD	C	TZD	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZD	C	TZD	C	TZD	C
Thiazide diuretics versus placebo/no treatment																						
ANBP-1 ¹³ CLTZ (1721) vs Placebo (1706)			3	3	98	109					17	31	1	2	8	18	25	35			NR/88.3 (NR/4)	NR/93.9 (NR/3.8)
ANBPS ¹⁵ CLTZ (293) vs Placebo (289)	37	48	23	28							8	12			2	5	7	9			134.7/88.6 (15/10)	145.9 /94 (15/10)
Barracough et al ¹⁶ BFTZ (58) vs Ca lactate (58)																	3	2	3	14	NR/90 (NR/10)	NR/104 (NR/10)
Carter ¹⁷ TZD (50) vs Control (49)															8	16	13	22	0	0		
EWPHE ¹⁸ HCTZ (416) vs Placebo (424)	63	116			7	16	7	17	4	3	16	22	4	1	67	93	135	149			150/85 (20/9)	171/95 (25/9)
HSCSG ²⁰ MCTZ (233) vs Placebo (219)	12	19			4	4	0	6	37	42							26	24				
HYVET ²¹ BFTZ (426) vs no treatment (426)									6	18					23	19	30	22			152/84 (13/7)	174/95 (11/6)
MRC-mild ²⁵ BFTZ (4297) vs Placebo (8654)	140	352	119	234					18	109					69	142	128	253			135/85 (15/10)	146/91 (15/10)
MRC-old ²⁶ Coamilozide (454) vs Placebo (926)	107	309	48	159					45	134					66	180	134	315	160	82	150/77 (15/10)	163/83 (15/10)
OSLO ²⁸ HCTZ (406) vs no treatment (379)	25	34	20	13	8	8			0	3	0	7					10	9				

Trial Intervention (N) vs Comparator (N)	All CV		CHD		MI		HF		Stroke		CRV		RF		CV death		All death		Withdraw due to AE		SBP/DBP	
	events														n						mmHg (SD)	
	TZD	C	TZD	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZD	C	TZD	C	TZD	C
PATS ²⁹ Indapamide (2841) vs Placebo (2824)	194	247	25	21					60	77							146	158			142.6/85.7 (16.9/8.7)	148.8/88.6 (19.1/10.1)
PHS ³⁰ CLTZ (193) vs Placebo (196)					7	6			0	2							2	2			131.5/88.4 (20/11.3)	147.4/98.4 (18.9/11.9)
SHEP ³² CLTD (2365) vs Placebo (2371)	289	414	140	184	65	100			106	163			2	2	90	112	213	242	307	166	144.0/67.6 (19.3/10.2)	155.1/71.1 (20.9/12.8)
SHEP-PS ³³ CLTD (443) vs Placebo (108)					8	2	6	2	11	6							32	7			142/68 (15/10)	157/71 (15/10)
VA-I ³⁴ HCTZ (73) vs Placebo (70)																	0	4			142.6/ 91.5 (15.4/5)	186.8/ 121 (17.2/4.7)
VA-II ³⁵ HCTZ (186) vs Placebo (194)													0	1			8	19	9	6	134.9/ 86.4 (15/10)	169.3/ 105.9 (15/10)
VA-NHLBI ³⁶ CLTD (508) vs Placebo (504)	25	13															2	0				
Thiazide diuretics versus angiotensin converting enzyme inhibitors																						
ALLHAT ¹² CLTD (15255) vs Lisinopril (9054)	3941	2514	1362	796			870	612	675	457			19 3	12 6			2203	1314	353	298	133.9/75.4 (15.2/9.8)	135.9/75.4 (17.9/10.7)
ANBP-2 ¹⁴ HCTZ (3039) vs Enalapril (3044)	736	695	195	173	82	58	78	69	107	112	163	152					210	195			142/79 (13/8)	141/79 (13/8)
HYVET ²¹ BFTZ (426) vs Lisinopril (431)									6	12					23	22	30	27			152/84 (13/7)	151/84 (13/7)
Thiazide diuretics versus α-β-blockers																						
HAPPHY ¹⁹ TZD (3272) vs Atenolol/Metoprolol			241	270			22	32	83	64							101	96	78	66	140/89 (15/10)	140/88 (15/10)

Trial Intervention (N) vs Comparator (N)	All CV		CHD		MI		HF		Stroke		CRV		RF		CV death		All death		Withdraw due to AE		SBP/DBP	
	events														n						mmHg (SD)	
	TZD	C	TZD	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZ D	C	TZD	C	TZD	C	TZD	C
(3297)																						
MAPHY ^{23,113} HCTZ/BFTZ (1625) vs Metoprolol (1609)	170	134	144	111	109	82									57	42	83	65			142/89 (15/10)	142/88 (15/10)
MRC-mild ²⁵ BFTZ (4297) vs Propranolol (4403)	140	146	119	103					18	42					69	65	128	120			135/85 (15/10)	137/85 (15/10)
MRC-old ²⁶ Coamilozide (454) vs Atenolol (456)	107	151	48	80					45	56					66	95	134	167	160	333	150/77 (15/10)	151/77 (15/10)
Thiazide diuretics versus calcium channel blockers																						
ALLHAT ¹² CLTD (15255) vs Amlodipine (9048)	3941	2432	1362	798			870	706	675	377			19 3	12 9			2203	1256	353	197	133.9/75.4 (15.2/9.8)	134.7/74.6 (14.9/9.9)
INSIGHT ²² Coamilozide (3286) vs Nifedipine (3289)					84	94	12	26	74	67			13	8			152	153	518	725	138/82 (14/8)	138/82 (14/8)
MIDAS ²⁴ HCTZ (441) vs Isradipine (442)	14	28	0	2	5	6			3	6							9	8			129.4/83.2 (16.4/5.0)	134/83.7 (16.8/5.2)
NICS-EH ²⁷ TMTZ (210) vs Nicardipine (204)	18	21			2	2	3	0	0	1	8	12							9	6	147/79 (16/9)	147/81 (15/8)
SHELL ³¹ CLTD (940) vs Lacidipine (942)	88	90			14	12	19	23	38	37							122	145			NR/80 (NR/10)	NR/80 (NR/10)
VHAS ³⁸ CLTD (707) vs Verapamil (707)	43	42	0	2	5	5			4	3	4	5					4	5	18	18	138.9/85 (10.5/5.0)	140.6/84.6 (10.4/5.1)

a: mean $\pm$ SD; b: mean $\pm$ SE; CV: cardiovascular events; CHD: coronary heart disease events; MI: myocardial infarction events; HF: heart failure events; CRV: cerebrovascular events; RF: renal failure; NR: not reported; DM: diabetes mellitus; AE: adverse events

TZD: thiazide/diuretics; BB: β -blockers; AB: α -blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; HCTZZ: hydrochlorothiazide; BFTZ: bendroflumethiazide or bendrofluazide; TMTZ: trichlormethiazide; CLTZ: chlorothiazide; MCTZ: methyclothiazide; C: comparators; CLTD: chlorthalidone

APPENDIX 13: QUALITY OF LIFE OUTCOMES FROM TRIALS RELATED TO THIAZIDE DIURETICS VERSUS PLACEBO OR NO TREATMENT AND OTHER ANTIHYPERTENSIVE DRUG CLASSES

Trials	Instruments used	Interventions	Data	Conclusion
ALPINE ³⁹ 1 year	Subjective Symptoms Assessment (SSA), 42 items, 7-grade Licker scale; 1: most positive	HCTZ	Emotional distress: 2.1 ± 1.0^a	No major differences in the SSA profile between treatments
			Sex life: 2.9 ± 1.0^a	
		Candesartan	Emotional distress: 2.0 ± 1.0^a	
			Sex life: 3.1 ± 1.1^a	
Bird et al ⁴⁰ 9 months	A package of tests for cognition	HCTZ + amiloride	Depression (%): 10.4	No significant differences between mean scores for psychometric tests or depression questionnaire, although blood pressure levels in treated groups fell significantly compared with placebo
			PALT ≤ 15 (%): 21.1	
			TMT timing $\geq 90s$ (%): 5.7	
		Atenolol	Depression (%): 10.4	
			PALT ≤ 15 (%): 19.9	
			TMT timing $\geq 90s$ (%): 5.9	
		Placebo	Depression (%): 9.2	
			PALT ≤ 15 (%): 18.5	
Boissel et al ⁴¹ 1 year	Subjective Quality-of-Life Profile questionnaire	Altizide + spironolactone		No significant differences between treatments after 9 months
		Bisoprolol		
		Enalapril		
		Verapamil		
Chang et al ⁴² 2 months	Sickness Impact Profile, Psychological General Well-Being Schedule, Sexual	TZD	Sexual dysfunction (scale: 0 to 16): 3.0 (7, 0) ^c , $p < 0.01$	Thiazide diuretic is associated with male sexual dysfunction; no differences were found between diuretic and placebo groups in measures of mood, general well-being,
			Psychological well-being (scale: 0 to 110): 84.0 (91, 76) ^c	

Trials	Instruments used	Interventions	Data	Conclusion
	Symptom Distress Index (SSDI)			ability to work, alertness and social activities
		Placebo	Sexual dysfunction (scale: 0 to 16): 0.0 (1, 0) ^c , $p < 0.01$	
			Psychological well-being (scale: 0 – 110): 84.3 (92, 78) ^c	
EWPHE ⁴³ 1 to 7 years	Quality of life questionnaire	HCTZ + triamterene	Depression (rate per 1000 person years): 14	Depression was more frequently reported in the actively treated group
		Placebo	Depression (rate per 1000 person years): 7.3	
Glik et al ⁴⁴ 4 months	Psychosocial well-being inventories and Spectrum of Physical Health Index	HCTZ + triamterene		There were no clinically or statistically significant differences between treatment groups for overall quality of life
		Metoprolol		
		Captopril		More patients on β -blockers than on diuretics reported of breathlessness, decreased physical capacity, cold hands and feet, slow heart rate, diarrhea, unusual tiredness and nightmares
HAPPY ¹⁹ 1 year	Quality of life questionnaire	TZD	Breathlessness (%): 8.0, $p=0.01$	
			Physical capacity decreased (%): 9.0, $p=0.011$	
			Cold hands and feet (%): 12.7, $p<0.001$	
			Slow heart rate (%): 1.5, $p<0.001$	
			Unusual tiredness (%): 15.4, $p=0.005$	
			Sleep dysfunction (%): 11.3	
			Nightmare (%): 4.0	
			Depression (%): 9.3	
		Atenolol or metoprolol		
			Breathlessness (%): 9.9, $p=0.01$	
			Physical capacity decreased (%): 11.0, $p=0.011$	
			Cold hands and feet (%): 21.4, $p<0.001$	
			Slow heart rate (%): 6.3, $p<0.001$	
			Unusual tiredness (%): 18.2, $p=0.005$	
			Sleep dysfunction (%): 10.9	
			Nightmare (%): 5.6	
			Depression (%): 9.3	
Lacourciere et al ⁴⁵ 12 weeks	Published well-being questionnaires	Indapamide	Score showed more favourable changes in sleep disorders	General well-being and subjective symptomatology improved with both treatments

Trials	Instruments used	Interventions	Data	Conclusion		
		Captopril	Scores showed more favourable changes in muscular or sensory asthenia and functional disturbances	Indapamide significantly improved sleep dysfunction		
Malmqvist et al ⁴⁶ 12 weeks	Subjective symptoms Assessment (SSA) profile, Psychological General Well-Being (PGWB) index, McMaster Overall Treatment Evaluation (OTE) questionnaire	HCTZ	Respiratory infection (%): 4	More dry cough with enalapril PGWB index and OTE questionnaire revealed no difference in overall QoL between treatment groups		
			Fatigue (%): 0			
			Headache (%): 10			
			Dizziness (%): 5			
			Palpitations (%): 0			
			Cough (%): 4			
		Enalapril	Respiratory infection (%): 5			
			Fatigue (%): 5			
			Headache (%): 19			
			Dizziness (%): 7			
			Palpitations (%): 0			
			Cough (%): 13			
		Candesartan	Respiratory infection (%): 8			
Fatigue (%): 8						
Headache (%): 7						
Dizziness (%): 4						
Palpitations (%): 4						
Cough (%): 0						
Martin et al ⁴⁷ 6 months	23-item quality of life questionnaire; scale 1to5 where 1: always, 5: never	HCTZ	Total (change from baseline): Mild: -0.02 Moderate: 0.10	The overall quality of life was better in Captopril group		
		Captopril	Total (change from baseline): Mild: 0.16 Moderate: 0.23			
Metelitsa et al ⁴⁸ 8 months	General well-being questionnaire	HCTZ	No change in terms of improvement of quality of life	Captopril had the best effect on quality of life		
		Captopril	Most effective			

Trials	Instruments used	Interventions	Data	Conclusion
		Nifedipine	Less effective	
		Propranolol	Less effective	
MRC-mild ⁴⁹ 2 years	Questionnaire modified from Bulpitt and Dollery	BFTZ (5 mg twice daily)	Impaired glucose tolerance (rate): M: 9.38; F: 6.01	Compared with placebo, Bendrofluazide treatment had higher incidence of impaired glucose tolerance, gout, impotence in men, constipation, and fatigue
			Gout (rate): M: 12.23; F: 1.06	
			Impotence (rate): M: 22.6; F: NA	
			Raynaud's phenomenon (rate):M: 0; F: 0.35	
			Skin disorder (rate): M: 0.41; F: 0.35	
			Difficult breathing (rate): M: 0; F: 0	
			Constipation (rate): M: 1.63; F: 2.12	
			Fatigue (rate): M: 6.93; F: 2.12	
			Nausea, dizziness, or headache (rate): M: 8.56; F: 16.27	
		Propranolol	Impaired glucose tolerance (rate): M: 3.65; F: 1.12	Compared with propranolol, Bendrofluazide treatment had higher incidence of impaired glucose tolerance, gout, impotence in men, and constipation, but lower incidence in skin disorder, difficult breathing, and fatigue
			Gout (rate): M: 2.56; F: 0	
			Impotence (rate): M: 5.48; F: NA	
			Raynaud's phenomenon (rate):M: 5.48; F: 5.62	
			Skin disorder (rate): M: 2.19; F: 1.87	
			Difficult breathing (rate): M: 8.04; F: 6.37	
			Constipation (rate): M: 0.37; F: 0	
			Fatigue (rate): M: 10.23; F: 15.00	
			Nausea, dizziness, or headache (rate): M: 6.57; F: 13.87	
		Placebo	Impaired glucose tolerance (rate): M: 2.51; F: 0.82	
			Gout (rate): M: 1.03; F: 0	
			Impotence (rate): M: 0.89; F: NA	
			Raynaud's phenomenon (rate):M: 0.15; F: 0	
			Skin disorder (rate): M: 0.15; F: 0	

Trials	Instruments used	Interventions	Data	Conclusion
			Difficult breathing (rate): M: 0.15; F: 0.33	
			Constipation (rate): M: 0; F: 0	
			Fatigue (rate): M: 0.30; F: 0.33	
			Nausea, dizziness, or headache (rate): M: 1.18; F: 2.12	
Ogihara et al ⁵⁰ 5 years	Quality of life questionnaire	TMTZ	Score improved for 1 item (headache) and worsened for 3 items (general symptoms, sleep scale and sexual function)	No significant differences between treatments in terms of total quality of life score
		Nicardipine	Score improved for 1 item (headache) and worsened for 1 item (cognitive function)	Nicardipine was tolerated slightly better than trichlormethiazide
Potempa et al ⁵¹ 4 weeks	Profile of Mood States and the Beck Depression Inventory	HCTZ		Mood values (anger, anxiety, confusion, depression, fatigue and vigour) were no different between treatments
		Beta-blockers (Pindolol, propranolol)		
SHELL ³¹ 5 years	Not reported	Chlorthalidone	Fatigue (%): 20.5 Edema (%): 4.9	Lacidipine treatment was associated with greater incidence of pretibial edema, whereas chlorthalidone treatment showed greater incidence of fatigue; other side effects similar between two groups
		Lacidipine	Fatigue (%): 13.7 Edema (%): 14.3	
SHEP ³² 4.5 years	Specified questionnaire	Chlorthalidone	Sexual dysfunction (%): 4.8 Sleep dysfunction (%): 26.4 Anxiety (%): 25.5 Memory trouble (%): 26.4 Depression (%): 10.7 Nightmare (%): 4.2 Loss appetite (%): 6.4	Psychosocial problems were greater in the active treatment group than in the placebo group
		Placebo	Sexual dysfunction (%): 3.2 Sleep dysfunction (%): 24.5 Anxiety (%): 24.1	

Trials	Instruments used	Interventions	Data	Conclusion
			Memory trouble (%): 20.4	
			Depression (%): 10.6	
			Nightmare (%): 3.7	
			Loss appetite (%): 5.5	
Slovick et al ⁵² 24 weeks	Quality of life questionnaire; Profile of mood states	BFTZ		The quality of life questionnaire scores improved with both treatments; no differences were observed between treatments with respect to sickness impact profile, profile of mood states or complaint rate categories
		Dilevalol		
Starr et al ⁵³ 24 weeks	Cognition was evaluated by a psychometric test battery	BFTZ		No significant differences between treatments were observed for psychometric or cognitive tests
		Captopril		
Suzuki et al ⁵⁴ 1 year	Sexual Symptoms Distress Index	TMTZ		All drugs except captopril caused sexual dysfunction
		Atenolol		
		Captopril		
Tedesco et al ⁵⁵ 26 months	Quality of life questionnaire	HCTZ		Compared with baseline, losartan group had significant improvement in quality of life, while no significant changes were observed in the HCTZ group
		Losartan		
TOHMS ^{56,116,117} 4 years	Quality of life questionnaire. Sexual dysfunction was scored by interviews	Chlorthalidone	General health: 1.5 ± 0.3^b	Improvements in quality of life were observed in all groups; greater improvements were in the chlorthalidone and the acebutolol groups Incidence of erection problem was relatively higher in the chlorthalidone group
			Energy or fatigue: 1.4 ± 0.2^b	
			Mental health: 2.7 ± 0.5^b	
			General function: 0.1 ± 0.2^b	
			Satisfaction with physical abilities: 0.4 ± 0.1^b	
			Social function: 0.2 ± 0.1^b Social contacts: -0.2 ± 0.1^b	

Trials	Instruments used	Interventions	Data	Conclusion
			Sexual dysfunction (% erection problem): 18.3	
		Acebutolol	General health: 2.2 ± 0.3^b	
			Energy or fatigue: 1.4 ± 0.2^b	
			Mental health: 3.1 ± 0.5^b	
			General function: 0.1 ± 0.1^b	
			Satisfaction with physical abilities: 0.4 ± 0.1^b	
			Social function: 0.2 ± 0.1^b	
			Social contacts: 0.1 ± 0.1^b	
			Sexual dysfunction (% erection problem): 11.8	
		Amlodipine	General health: 0.6 ± 0.4^b	
			Energy or fatigue: 0.7 ± 0.2^b	
			Mental health: 2.0 ± 0.6^b	
			General function: 0.1 ± 0.1^b	
			Satisfaction with physical abilities: 0.5 ± 0.1^b	
			Social function: 0.1 ± 0.1^b	
			Social contacts: 0.4 ± 0.1^b	
			Sexual dysfunction (% erection problem): 15.0	
		Doxazosin	General health: 1.2 ± 0.3^b	
			Energy or fatigue: 0.5 ± 0.2^b	
			Mental health: 1.6 ± 0.5^b	
			General function: -0.3 ± 0.1^b	
			Satisfaction with physical abilities: 0.3 ± 0.1^b	
			Social function: 0.0 ± 0.1^b	
			Social contacts: 0.0 ± 0.1^b	
			Sexual dysfunction (% erection problem): 11.1	
		Enalapril	General health: 0.8 ± 0.3^b	
			Energy or fatigue: 0.8 ± 0.2^b	

Trials	Instruments used	Interventions	Data	Conclusion
			Mental health: 1.3 ± 0.5^b	
			General function: -0.1 ± 0.1^b	
			Satisfaction with physical abilities: 0.4 ± 0.1^b	
			Social function: 0.1 ± 0.1^b	
			Social contacts: 0.1 ± 0.1^b	
			Sexual dysfunction (% erection problem): 14.1	
		Placebo	General health: 1.0 ± 0.3^b	
			Energy or fatigue: 0.7 ± 0.2^b	
			Mental health: 1.4 ± 0.4^b	
			General function: -0.3 ± 0.1^b	
			Satisfaction with physical abilities: 0.3 ± 0.1^b	
			Social function: -0.1 ± 0.1^b	
			Social contacts: 0.2 ± 0.1^b	
			Sexual dysfunction (% erection problem): 16.7	
VA-II ³⁵ 3.7 years	Not reported	HCTZ + reserpine or HCTZ (tid)	Sexual dysfunction (n/N): 1/186	No apparent differences of reported dysfunctions between treatments
			Depression (n/N): 7/186	
			Other dysfunction (n/N): 6/186	
		Placebo	Sexual dysfunction (n/N): 1/194	
			Depression (n/N): 5/194	
			Other dysfunction (n/N): 0/194	
VA-NHLBI ³⁶ 7.5 years	Interview at each visit	Chlorthalidone + reserpine	Energy or fatigue (%): 13	Chlorthalidone treatment had higher incidence of fatigue, sexual dysfunction and psychological problems than placebo
			Sexual dysfunction (%): 18	
			Psychological problem (%): 6.5	
		Placebo	Energy or fatigue (%): 7	
			Sexual dysfunction (%): 6	
			Psychological problem (%): 5.6	
Vanmolkot et al ⁵⁷	Quality of life questionnaire	Bendroflumazide		No differences were found between treatments for quality of life

Trials	Instruments used	Interventions	Data	Conclusion
8 weeks		Bisoprolol		
VHAS ³⁸	Not reported	Chlorthalidone	Energy or fatigue (%): 8.4	Constipation and sexual dysfunction were more frequent with verapamil while lack of energy was more frequent with chlorthalidone
2 years			Constipation (%): 3.1	
			Sexual dysfunction (%): 1.7	
		Verapamil	Energy or fatigue (%): 4.7	
Constipation (%): 13.7				
Sexual dysfunction (%): 2.4				
Wassertheil-Smoller et al ⁵⁸	Quality of life questionnaire	Chlorthalidone		Low dose of chlorthalidone and atenolol improved quality of life, however, chlorthalidone increased sexual problems in men
6 months				
		Atenolol		
		Placebo		

PALT, Paired Associate Learning Test (a score of 15 or less out of a maximum of 18 indicates impairment); TMT, Trail-Making Test (a timed test measures alertness and speed of reaction, a timing of > 60s for completion of the trail is considered abnormal; a, mean $\pm$ SD; b, mean change from baseline $\pm$ SE; c, median (75th and 25th percentile)

TZD: thiazide/diuretics; BB: β -blockers; AB: α -blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; HCTZ: hydrochlorothiazide; BFTZ: bendroflumethiazide or bendrofluazide; TMTZ: trichlormethiazide; CLTZ: chlorothiazide; MCTZ: methyclothiazide

APPENDIX 14: CLINICAL OUTCOMES FROM TRIALS RELATED TO BP TARGET

Trial	Moderate			Intense		
	Blood pressure	Kidney function	Adverse events	Blood pressure	Kidney function	Adverse events
AASK ^{59,68}	SBP: 141 ± 12 ^a	GFR decline: - 1.95 ± 0.17 ^b , NS	All death: 33	SBP: 128 ± 12	GFR decline: - 2.21 ± 0.17 ^b , NS	All death: 29
	DBP: 85 ± 7 ^a	RF: 69		DBP: 78 ± 8	RF: 61	
ABCD-H ⁶⁰	SBP: 138 ± 15 ^a	CC: 52.6 ± 5.8 ^b , NS	All death: 25	SBP: 132 ± 15 ^a	CC: 56.8 ± 5.8 ^b , NS	All death: 13
	DBP: 86 ± 10 ^a		MI: no difference	DBP: 78 ± 10 ^a		MI: no difference
			CHD: no difference			CHD: no difference
			CRV: no difference			CRV: no difference
			Retinopathy: 79			Retinopathy: 71
ABCD-N ⁶¹	SBP: 137 ± 0.7 ^b (10.9 ^a)	CC: no difference	All death: 20	SBP: 128 ± 0.8 ^b (12.5 ^a)	CC: no difference	All death: 18
	DBP: 81 ± 0.3 ^b (4.6 ^a)		CV death: 9	DBP: 75 ± 0.3 ^b (4.6 ^a)		CV death: 13
			MI: 15			MI: 19
			CHD: 11			CHD: 12
			Stroke: 13			Stroke: 4
CSG ⁶²	MAP: 100 to 107	CC: 58		MAP: ≤ 92	CC: 54	
		Proteinuria (mg/24h): 1723			Proteinuria (mg/24h): 535, p=0.02 vs moderate	
HOT ^{63,114}	SBP: 143.7 ± 11.3 ^a	SC: 1.02 ± 0.36 ^b	All death: 188	SBP: 139.7 ± 11.7 ^a	SC: 1.01 ± 0.33 ^b , NS	All death: 207
	DBP: 85.2 ± 5.1 ^a		CV death: 87	DBP: 81.1 ± 5.3 ^a		CV death: 96
			Stroke: 94			Stroke: 89
			MI: 127			MI: 107
			CV: 274			CV: 263
Ikeda et al ⁶⁴	SBP: 128 ± 4 ^b (21.2 ^a)	RF: 12	All death: 3	SBP: 118 ± 4 ^b (21.2 ^a)	RF: 6	All death: 2
	DBP: 81 ± 2 ^b (10.6 ^a)	SC: 2.5 ± 0.7 ^b		DBP: 73 ± 3 ^b (15.9 ^a)	SC: 1.9 ± 0.6 ^b , p< 0.05	

Trial	Moderate			Intense		
	Blood pressure	Kidney function	Adverse events	Blood pressure	Kidney function	Adverse events
		CC: 35 ± 3^b			CC: 40 ± 3^b , $p < 0.05$	
MDRD ⁶⁵	SBP: 133.8 ± 14.9^a	RF: 286	All death: 26	SBP: 126.2 ± 13.6^a	RF: 268	All death: 44
	DBP: 80.7 ± 7.2^a			DBP: 76.9 ± 6.4^a		
REIN-2 ⁶⁶	SBP: 134 ± 15^a	RF: 34	All death: 3	SBP: 130 ± 15^a	RF: 38	All death: 2
	DBP: 82 ± 10^a	GFR decline: - 0.24		DBP: 80 ± 10^a	GFR decline: - 0.22	
		CC decline: -0.25			CC decline: -0.26	
Toto et al ⁶⁷	SBP: 138 ± 2^b (11.8 ^a)	RF: 2	All death: 0	SBP: 133 ± 3^b (17.7 ^a)	RF: 7	All death: 1
	DBP: 87 ± 1^b (6.5 ^a)	GFR decline: -0.05 ± 0.50^b		DBP: 81 ± 1^b (6.5 ^a)	GFR decline: -0.31 ± 0.45^b , NS	

a: mean $\pm$ SD; b: mean $\pm$ SE; SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); GFR: glomerular filtration rate (ml/min/1.73 m²); NS: not statistically significant between treatments; CC: creatinine clearance (ml/min/1.73 m²); SC: serum creatinine (mg/dl); MI: myocardial infarction events; CHD: coronary heart disease events; CRV: cerebrovascular events; MAP: mean arterial pressure (mmHg); CV: cardiovascular events; RF: renal failure (even

APPENDIX 15: LITERATURE SEARCH STRATEGY FOR COST EFFECTIVENESS STUDIES

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
Ovid Multifile Search MEDLINE® (1966-present; In-Process & Other Non-Indexed Citations) BIOSIS Previews® (1985-present) EMBASE® (1980-present)	Date: (up to 18 May 2007)	<i>Concept #1 (Thiazide Diuretics) from Clinical Search Strategy</i> AND <i>Concept #2 (Hypertension) from Clinical Search Strategy</i> AND <i>Concept #3 (Economic Filter)</i> 3. Economics.sh. OR exp Costs and Cost Analysis/ OR Value of Life.sh. OR exp Economics, Medical/ OR exp Economics, Hospital/ OR Economics, Nursing.sh. OR Economics, Pharmaceutical.sh. OR exp Fees and Charges/ OR Budgets.sh. OR exp Models, Economic/ OR Markov Chains.sh. OR Monte Carlo Method.sh. OR Decision Trees.sh. OR Quality of Life.sh. OR Patient Satisfaction.sh. OR Quality-Adjusted Life Years.sh. [MeSH headings for MEDLINE®] OR exp Health economics/ OR exp Economic Evaluation/ OR exp Pharmacoeconomics/ OR exp Economic Aspect/ OR Quality Adjusted Life Year.sh. OR exp Quality of Life/ [EMTREE terms for EMBASE®] OR (Economic Impact OR Economic Value OR Pharmacoeconomics OR Health Care Cost OR Economic Factors OR Economics OR Cost Analysis OR Cost OR Economic Analysis OR Cost-Effectiveness OR Costs OR "Quality of Life" OR Health Care Cost OR Cost Savings OR Cost-Benefit Analysis OR Hospital Costs OR Medical Costs OR Quality-of-Life).mp. [unqualified search for BIOSIS®] OR

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		(econom\$ OR cost OR costly OR costing OR costed OR costs OR price OR prices OR pricing OR priced OR discount OR discounts OR discounted OR discounting OR expenditure OR expenditures OR budget\$ OR afford\$ OR pharmacoeconomic\$ OR (pharmaco ADJ1 economic\$) OR (decision ADJ1 (tree\$ OR analy\$ OR model\$)) OR ((value OR values OR valuation) ADJ2 (money OR monetary OR life OR lives)) OR QOL OR QOLY OR QOLYs OR HRQOL OR QALY OR QALYs (quality ADJ1 life) OR (willingness ADJ1 pay) OR (quality ADJ1 (adjusted life year\$))).ti,ab. <i>[Textwords searched in title, abstract]</i>
PubMed	Date: (up to 1 May 2007)	Same MeSH and keywords as per Ovid MEDLINE® search. Appropriate syntax used.
Cochrane Library (Issues 2, 3, 4, 2006; Issue 1, 2007)		Same MeSH and keywords as per Ovid MEDLINE® search, excluding study design filter. Appropriate syntax used.
OHE-IFPMA Database Ltd. HEED: Health Economic Evaluations Database		Same MeSH and keywords as per Ovid MEDLINE® search, excluding study design filter. Appropriate syntax used.
Websites of health economics research groups		Health Economics Research Group (HERG); Health Economics Research Unit (HERU); etc.

APPENDIX 16: PREVIOUS ECONOMIC EVALUATIONS OF HYPERTENSION DRUG TREATMENT STUDIES INCLUDING THIAZIDE DIURETICS

Author	Country	Year	Type of Analysis	Study Population	Comparators	Outcome Measures	Results
Baio G et al ⁸⁹	Italy	2003	Cost effectiveness analysis	Newly diagnosed hypertensive patients over 20 years of age	CCB - amlodipine Beta blocker - atenolol ACEI - fosinopril Diuretic - indapamide ARB - losartan	Effective treatment defined as persistence with therapy at recommended dosage on 273rd day after first prescription. Costs included only the direct costs of drugs. Posterior probability of an effective antihypertensive treatment	The mean probability of potential effectiveness was highest for losartan with a value of 0.1836 as compared with atenolol (0.1527), indapamide (0.1365), amlodipine (0.1280) and fosinopril (0.0840).
Burns R ⁸⁵	US	1989	Cost effectiveness analysis	Elderly hypertensive patients	Stepped care beginning with thiazide therapy - HCTZ vs Potassium-sparing diuretic initial therapy versus CCB initial therapy versus ACEI initial therapy	Cost per 1000 patient treatment years and cardiovascular death prevented	Based on both the cost per 1000 patient treatment years and cardiovascular deaths prevented initial therapy with thiazides was significantly more cost effective than potassium sparing diuretics, CCBs and ACEIs.
Chen GJ et al ⁸⁶	US	2005	Cost effectiveness analysis	Men and women 60 years and older with isolated systolic hypertension	Stepped care approach beginning with thiazides therapy - chlorthalidone followed by addition of a beta blocker - atenolol or reserpine as compared with single therapy with beta blocker - atenolol, ACEI -	Cost of 5 year NNT to prevent one adverse cardiovascular disease event	The cost for 5 years to prevent one adverse CVD event was lowest for stepped care chlorthalidone therapy with a cost of \$6843. Other therapies costs ranged from \$13215 to \$45,510.

Author	Country	Year	Type of Analysis	Study Population	Comparators	Outcome Measures	Results
					enalapril, alpha blocker - terazosin, or CCB – nifedipine.		
Edelson JT et al ⁸¹	US	1990	Cost effectiveness analysis	Persons aged 35 through 64 years with diastolic blood pressure of 95 mm Hg or greater.	Thiazide - HCTZ, CCB - nifedipine, Alpha blocker - prazosin, ACEI – captopril.	Year of life saved.	The cost per year of life saved over a 20 year simulation period was the lowest for propranolol followed by HCTZ, nifedipine, prazosin and captopril.
Fretheim A et al ⁹²	Canada, France, Germany, Norway, the UK and the US	2003	Cost minimization analysis	Hypertensive patients in Canada, France, Germany, Norway the UK and the US	Existing treatment versus thiazide therapy	Potential drug-cost savings of switching patients, who are suitable candidates for thiazide-therapy but are receiving other hypertension treatments, to thiazides	The estimated potential annual cost savings associated with switching appropriate patients to thiazides therapy in Canada were US\$13.8 million.
Hilleman DE et al ⁹⁰	US	1994	Cost minimization analysis	Newly diagnosed mild to moderate diastolic hypertensives	Diuretics Beta blockers Centrally acting alpha agonists Alpha blockers CCBs ACE inhibitors	Cost including acquisition cost, supplemental drug acquisition cost, laboratory monitoring, clinic visits and treatment of side effects.	Beta blockers were associated with the lowest total costs for the treatment of mild to moderate diastolic hypertensives followed by diuretics, centrally acting alpha agonists, ACEIs, alpha blockers and CCBs.
Johannesson M et al ⁸³	Sweden	1993	Cost effectiveness analysis	Middle aged men with mild to moderate uncomplicated hypertension	Beta blocker - metoprolol versus thiazides diuretics	Life year gained	When direct and indirect costs of morbidity were included metoprolol was shown to be cost-saving compared with thiazides diuretics. When only direct costs were included, the cost per life-year gained was \$US2400.

Author	Country	Year	Type of Analysis	Study Population	Comparators	Outcome Measures	Results
Johannesson M ⁸²	Sweden	1996	Cost effectiveness analysis	Hypertensive patients in Sweden	ACEI, CCBs, beta blockers and diuretics	Life year gained	Treatment of middle aged (45 to 69 years) men and women and older men and women (≥ 70 years) with a DBP ≥ 90 mmHg was cost effective; however, it was questionable whether it was in general cost-effective to treat younger men and women with mild hypertension. ACEI and CCBs were more cost effective than beta blockers and diuretics only under the most optimistic assumptions of their efficacy and only in those at high risk of coronary heart disease.
Kawachi I, Malcolm LA ⁷⁹	New Zealand	1991	Cost utility analysis	Mild-to-moderate hypertension (DBP 90 to 114 mmHg)	Diuretic, beta-blocker, ACEI	QALY	Diuretic monotherapy was the most cost-effective followed by beta blockers, then ACEIs. The cost effectiveness of anti-hypertensive therapy ranged from £11058 to £63760 per QALY gained in men and from £22060 to £194989 per QALY gained in women.
Linjer E et al ⁹¹	Sweden	2005	Cost minimization analysis	Elderly (age 70 to 84 years) patients with hypertension who participated in the Swedish Trial in Old Patients with Hypertension-2	Diuretics versus beta blockers versus CCBs versus ACEI	Overall costs including those associated with the protocol, non-protocol driven costs and drug treatment costs	Total costs for management of hypertension were lower with diuretics, beta-blockers and CCBs as compared with ACEIs.
National Collaborating Centre for	UK	2006	Cost utility analysis	Hypertensive patients aged 55 years and older.	ACEI, ARBs, Beta blockers, CCBs versus thiazides-type	QALY	This study found that calcium channel blockers were the most cost effective initial

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Chronic Conditions ⁷⁷					diuretics		therapy for this population.
Nordmann AJ et al ⁷⁸	Canada	2003	Cost utility analysis	Men aged 40 years without cardiovascular comorbidity requiring antihypertensive drug therapy	ACEI versus Beta blocker and/or diuretics (conventional therapy) versus Risk stratification by electrocardiography (ECG) and individualized therapy (ACEI in presence of LVH, else conventional therapy) versus Risk stratification by echocardiography and individualized therapy (ACEI in presence of LVH, else conventional therapy)	QALY	Conventional therapy was more cost effective than any of the alternative strategies for treatment with ACEIs.
Pearce KA et al ⁸⁷	US	1998	Cost effectiveness analysis	Separate analysis for middle aged and elderly patients with uncomplicated mild to moderate hypertension.	Thiazides - HCTZ Beta-blocker - atenolol and propranolol ACEI - enalapril andtrandolapril CCB - nifedipine GITS and nisoldipine - most commonly prescribed in each class and the least expensive	One major event – MI or stroke or death	This cost minimization analysis found that treatment with diuretics was the most cost effective in these patients. Beta blockers were slightly less cost effective whereas ACEI, CCB and alpha-blockers were significantly less cost effective.
Plans-Rubio, P ⁸⁰	Spain	1998	Cost effectiveness analysis	Individuals aged 30 to 69 years with mild to severe hypertension.	Smoking cessation therapy versus cholesterol lowering medications versus	Life year gained	Smoking cessation therapies most cost effective followed by antihypertensive drug therapy. HCTZ and

Author	Country	Year	Type of Analysis	Study Population	Comparators	Outcome Measures	Results
					antihypertensive drug treatment		propranolol were cost effective for moderate/severe hypertension and HCTZ and nifedipine were for mild hypertension.
Ramsey SD et al ⁸⁸	US	1999	Cost effectiveness analysis	Newly diagnosed mild hypertension	ACEI - enalapril CCB - amlodipine Beta blocker - acebutolol Thiazide - chlorthalidone	Effectiveness as measured by the number of patients who achieve control on initial therapy.	Initial costs to achieve and maintain hypertension control were lowest for chlorthalidone followed by acebutolol, amlodipine, and enalapril. Although a slightly higher percentage of patients will achieve control with CCBs, it is at a substantially higher cost than with chlorthalidone
Staflas PC et al ⁸⁴	Greece	2005	Cost effectiveness analysis	Mild-to-moderate hypertensive patients in Greece	Thiazide - chlorthalidone Beta blocker - propranolol CCB - amlodipine ACEI - enalapril ARB - losartan	Death prevented	Chlorthalidone was the most cost effective treatment followed by propranolol, amlodipine, enalapril and losartan.

HCTZ – hydrochlorothiazide

CCB – calcium channel blocker

ACEI – angiotensin converting enzyme inhibitors

ARB - angiotensin receptor blockers