BLOOD PRESSURE CONTROL IN ACUTE ISCHEMIC STROKE

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Rationale for Acute Blood Pressure Control

- Reduce risk of bleeding (hemorrhagic transformation)
- Reduce development of cerebral edema
- Reduce risk of acute cardiac event
- Reduce development of systemic hypertensive complications (renal, eye, etc.)

Reasons to not reduce BP acutely

- Worsen initial stroke
  - Ischemic penumbra
  - Other at-risk tissue and areas
- Impair normal physiologic response
  - In many patients BP falls spontaneously within 24-48 hours

Prior Studies

- Numerous studies and trials dating back 20-30 years
- Some described a 'U' or 'J' shaped curve
- Several medications studies
  - Nimodipine
  - Candasartan
  - Labetalol
  - ACE-I
- All with conflicting results

New Study

Effects of Immediate Blood Pressure Reduction on Death and Major Disability in Patients With Acute Ischemic Stroke
The CATIS Randomized Clinical Trial

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JAMA, 2014

CATIS Design

- 4071 patients
- Ischemic stroke
- Rx within 48 hours of Sx onset
- Elevated BP
- Single blind Rx; blinded endpoints
- TPA treatment excluded

Goals

- Reduce BP by 10-25% within 24 hours of randomization
- Achieve and maintain BP < 140/90 for 7 days
- Or discontinue all BP medications

- Treatments were ACE-inhibitors, Ca++ blockers, diuretics

Primary Outcomes

- **Death or major disability at 14 days (or hospital discharge)**
- **Major disability defined as mRS of 3-5**
- **Disability at 3 months**

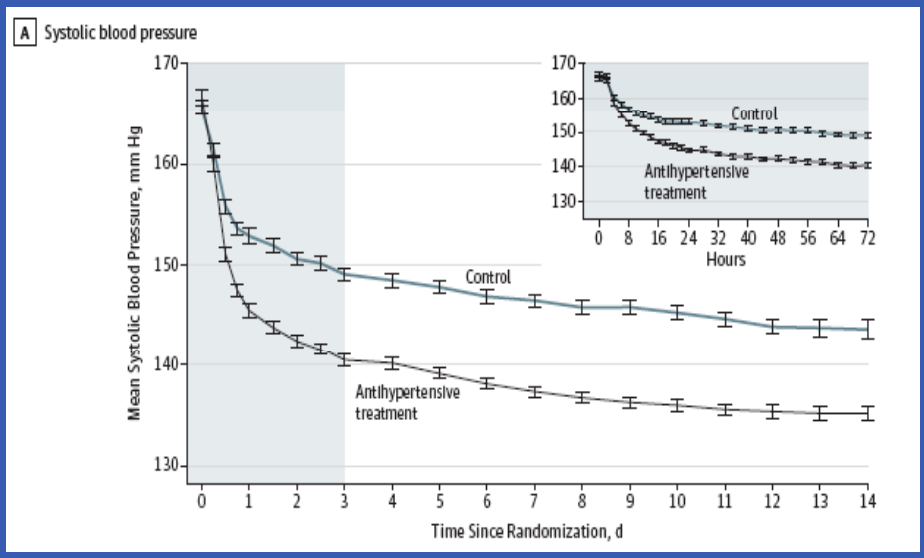
Results

- > 22,000 patients screened
- > 18,000 patients excluded
- 4071 randomized

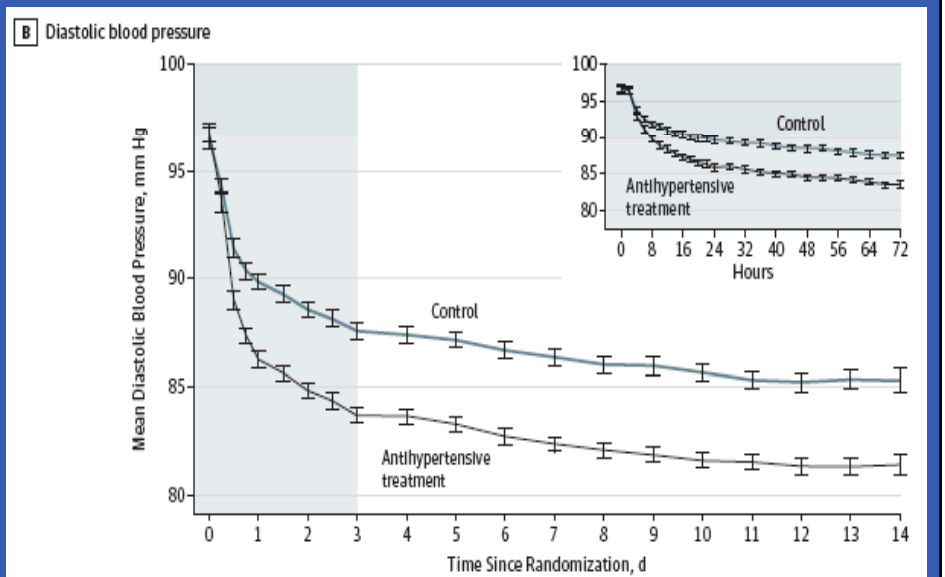
Patient Population

Characteristics	Antihypertensive Treatment (n = 2038)	Control (n = 2033)
Age, mean (SD), y	62.1 (10.8)	61.8 (11.0)
Men, No. (%)	1317 (64.6)	1287 (63.3)
Time from onset to randomization, mean (SD), h	15.3 (12.9)	14.9 (13.0)
Blood pressure at entry, mean (SD), mm Hg		
Systolic	166.7 (17.3)	165.6 (16.5)
Diastolic	96.8 (10.8)	96.5 (11.4)
Body mass index, mean (SD)[a]	24.9 (3.2)	25.0 (3.1)
NIHSS score, median (IQR)[b]	4.0 (2.0-7.0)	4.0 (3.0-8.0)
History of hypertension, No. (%)	1610 (79.0)	1599 (78.7)
Current use of antihypertensive medications, No. (%)	1014 (49.8)	983 (48.4)
Hyperlipidemia, No. (%)	137 (6.7)	140 (6.9)
Diabetes mellitus, No. (%)	369 (18.1)	350 (17.2)
Coronary heart disease, No. (%)	216 (10.6)	228 (11.2)
Current cigarette smoking, No. (%)	725 (35.6)	760 (37.4)
Current alcohol drinking, No. (%)	614 (30.1)	639 (31.4)
Ischemic stroke subtype, No. (%)[c]		
Thrombotic	1575 (77.3)	1595 (78.5)
Embolic	99 (4.9)	103 (5.1)
Lacunar	417 (20.5)	385 (18.9)

Blood Pressure Results



Blood Pressure Results

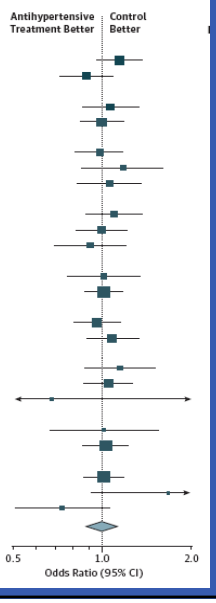


Primary and Secondary Outcomes

Primary outcome				
Death or major disability, No. (%)[a]	683 (33.6)	681 (33.6)	1.00 (0.88 to 1.14)	.98
Secondary outcomes				
Score on modified Rankin scale[b], median (IQR)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)		.70
Participants, No. (%)				
0 (no symptoms)	204 (10.0)	154 (7.6)	0.98 (0.88 to 1.09)[c]	.70
1 (no significant disability despite symptoms)	653 (32.2)	701 (34.6)		
2 (slight disability)	491 (24.2)	491 (24.2)		
3 (moderate disability)	292 (14.4)	297 (14.7)		
4 (moderately severe disability)	258 (12.7)	285 (14.1)		
5 (severe disability)	108 (5.3)	77 (3.8)		
6 (dead)	25 (1.2)	25 (1.2)		
Death, No. (%)	25 (1.2)	25 (1.2)	1.00 (0.57 to 1.74)	.99
Duration of initial hospitalization, median (IQR), d	13.0 (9.0 to 14.0)	13.0 (9.0 to 14.0)		.28

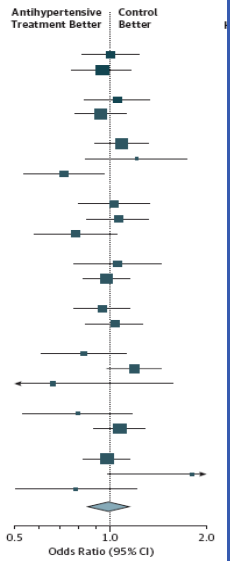
Primary Outcome by Group

	Antihypertensive Treatment		Control		
Subgroup	Total, No.	Events, No. (%)	Total, No.	Events, No. (%)	Odds Ratio (95% CI)
Age, y					
<65	1198	352 (29.4)	1203	325 (27.0)	1.12 (0.94-1.34)
≥65	833	331 (39.7)	824	356 (43.2)	0.87 (0.71-1.05)
Sex					
Women	715	267 (37.3)	743	269 (36.2)	1.05 (0.85-1.30)
Men	1316	416 (31.6)	1284	412 (32.1)	0.98 (0.83-1.15)
Time to randomization, h					
<12	1015	376 (37.0)	1082	412 (38.1)	0.96 (0.80-1.14)
12-23	401	132 (32.9)	331	99 (29.9)	1.15 (0.84-1.57)
≥24	609	172 (28.2)	609	167 (27.4)	1.04 (0.81-1.34)
Baseline SBP, mm Hg					
<160	715	225 (31.5)	765	228 (29.8)	1.08 (0.87-1.35)
160-179	838	288 (34.4)	851	297 (34.9)	0.98 (0.80-1.19)
≥180	478	170 (35.6)	411	156 (38.0)	0.90 (0.69-1.19)
History of hypertension					
No	428	150 (35.0)	430	151 (35.1)	1.00 (0.75-1.32)
Yes	1603	533 (33.3)	1597	530 (33.2)	1.00 (0.87-1.16)
Use of antihypertension medications					
No	1022	354 (33.8)	1045	366 (35.0)	0.95 (0.79-1.13)
Yes	1009	338 (33.5)	982	315 (32.1)	1.07 (0.88-1.29)
Baseline NIHSS score					
0-4	1065	134 (12.6)	1009	113 (11.2)	1.14 (0.87-1.49)
5-15	871	460 (52.8)	923	479 (51.9)	1.04 (0.86-1.25)
≥16	95	89 (93.7)	93	89 (95.7)	0.67 (0.18-2.44)
Baseline Rankin score					
<3	914	47 (5.1)	900	46 (5.1)	1.01 (0.66-1.53)
≥3	1117	636 (56.9)	1125	635 (56.4)	1.02 (0.86-1.21)
Stroke subtype					
Thrombolic	1513	539 (35.6)	1540	544 (35.3)	1.01 (0.87-1.18)
Embolic	93	60 (64.5)	92	48 (52.2)	1.67 (0.92-3.01)
Lacunar	366	66 (18.0)	338	78 (23.1)	0.73 (0.51-1.06)
Overall	2031	683 (33.6)	2027	681 (33.6)	1.00 (0.88-1.14)



Three Month Outcomes

Subgroup	Antihypertensive Treatment Total, No.	Antihypertensive Treatment Events, No. (%)	Control Total, No.	Control Events, No. (%)	Odds Ratio (95% CI)
Age, y					
<65	1172	224 (19.1)	1182	223 (18.9)	1.02 (0.83-1.25)
≥65	816	276 (33.8)	805	279 (34.7)	0.96 (0.78-1.18)
Sex					
Women	701	196 (28.0)	726	193 (26.6)	1.07 (0.85-1.35)
Men	1287	304 (23.6)	1261	309 (24.5)	0.95 (0.79-1.14)
Time to randomization, h					
<12	993	298 (30.0)	1054	295 (28.0)	1.10 (0.91-1.34)
12-23	392	92 (23.5)	328	66 (20.1)	1.22 (0.85-1.74)
≥24	597	108 (18.1)	600	139 (23.2)	0.73 (0.55-0.97)
Baseline SBP, mm Hg					
<160	702	155 (22.1)	754	162 (21.5)	1.04 (0.81-1.33)
160-179	820	223 (27.2)	830	215 (25.9)	1.07 (0.86-1.33)
≥180	466	122 (26.2)	403	125 (31.0)	0.79 (0.59-1.06)
History of hypertension					
No	420	107 (25.5)	425	104 (24.5)	1.06 (0.77-1.44)
Yes	1568	393 (25.1)	1562	398 (25.5)	0.98 (0.83-1.15)
Use of antihypertension medications					
No	1004	256 (25.5)	1033	273 (26.4)	0.95 (0.78-1.16)
Yes	984	244 (24.8)	954	229 (24.0)	1.04 (0.85-1.28)
Baseline NIHSS score					
0-4	1050	89 (8.5)	993	100 (10.1)	0.83 (0.61-1.12)
5-15	848	335 (39.5)	901	320 (35.5)	1.19 (0.98-1.44)
≥16	90	76 (84.4)	92	82 (89.1)	0.66 (0.28-1.58)
Baseline Rankin score					
<3	900	50 (5.6)	883	61 (6.9)	0.79 (0.54-1.17)
≥3	1088	450 (41.4)	1103	441 (40.0)	1.06 (0.89-1.26)
Stroke subtype					
Thrombolic	1482	392 (26.5)	1513	408 (27.0)	0.97 (0.83-1.15)
Embolic	89	47 (52.8)	88	34 (38.6)	1.78 (0.98-3.23)
Lacunar	362	48 (13.3)	329	54 (16.4)	0.78 (0.51-1.19)
Total	1988	500 (25.2)	1987	502 (25.3)	0.99 (0.86-1.15)



2013 Guidelines

trials with well-defined criteria are needed. At this time, the previous recommendation not to lower the blood pressure during the initial 24 hours of acute ischemic stroke unless the blood pressure is >220/120 mm Hg or there is a concomitant specific medical condition that would benefit from blood pressure lowering remains reasonable.

Jauch et al., Stroke, 2013

What to do about BP after 24 hours?

- Largely a data-free zone
- Do not lower it if patient is neurologically or hemodynamically unstable
  - Could worsen stroke
- Do not lower if patient has a known high-grade large vessel stenosis
  - Unclear how to assess small vessel stenosis
- DANGER of stopping certain BP meds
  - B-blocker, clonidine
- AVOID ACE-I if patients will receive or have received TPA
  - Risk of angioedema

Unintended Consequences

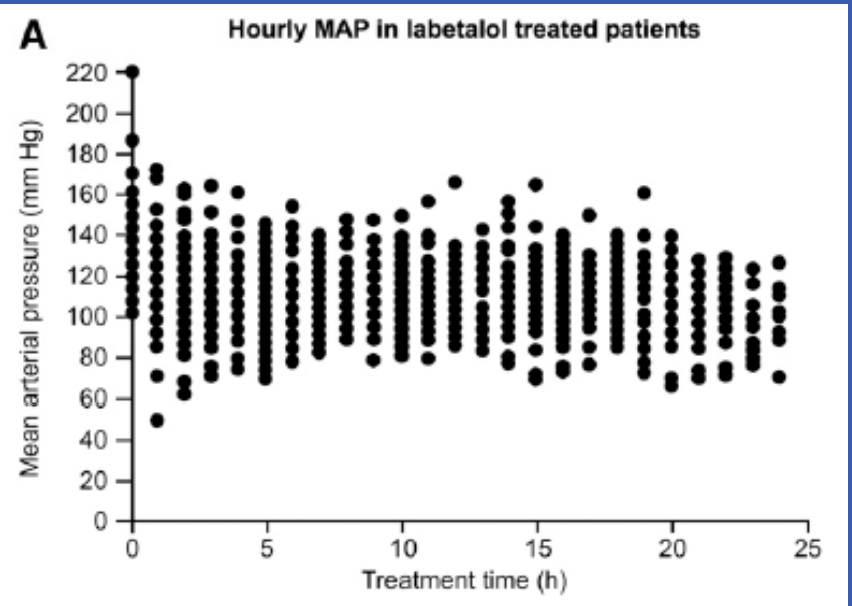
- Patient is discharged on no BP meds
- PCPs may feel that treatment of HTN is not necessary since it was not done in hospital
- Clearly this is the WRONG public health message
- Consensus is to begin a BP medication once stable especially if patient had a Hx of HTN

Optimal Approaches

Controlled blood pressure lowering during acute stroke can best be achieved with intravenous antihypertensive therapies. A single optimal medication to lower the blood pressure in all patients with acute stroke has not been determined, and an individualized approach is best.

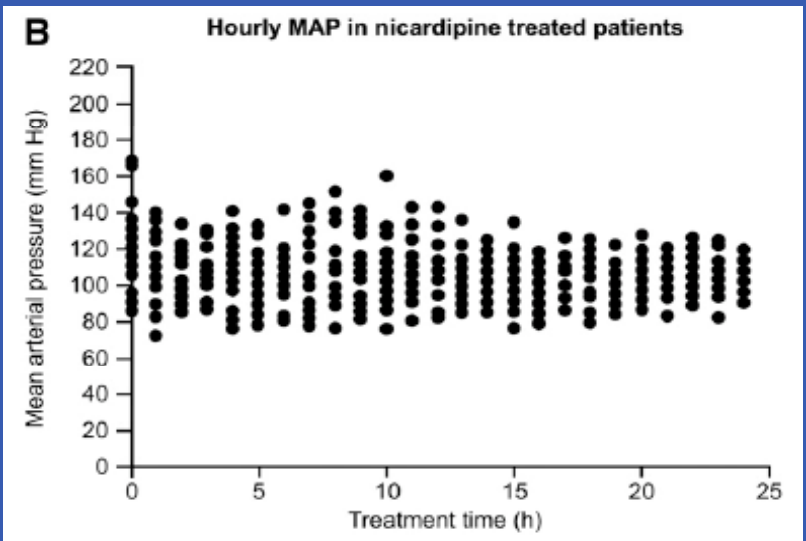
Jauch et al., Stroke, 2013

Labetalol vs Nicardipine



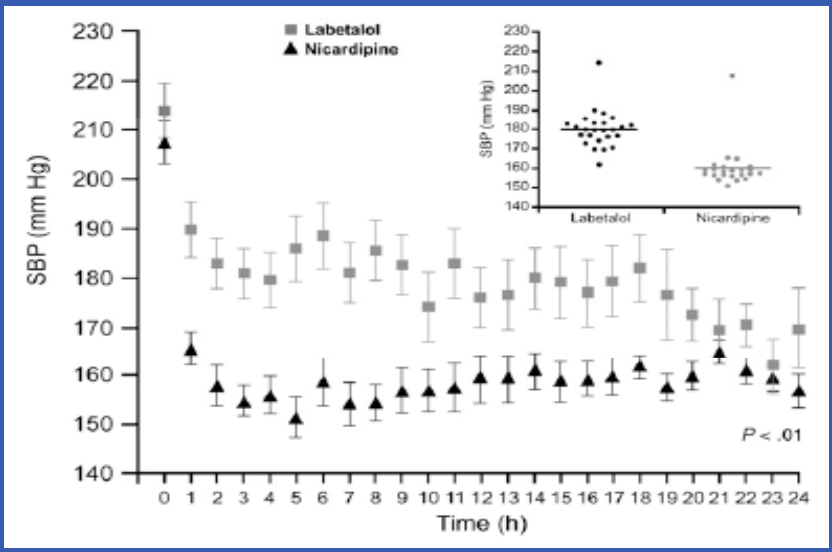
Peacock et al, Am J Emerg Med, 2012

Nicardipine Rx



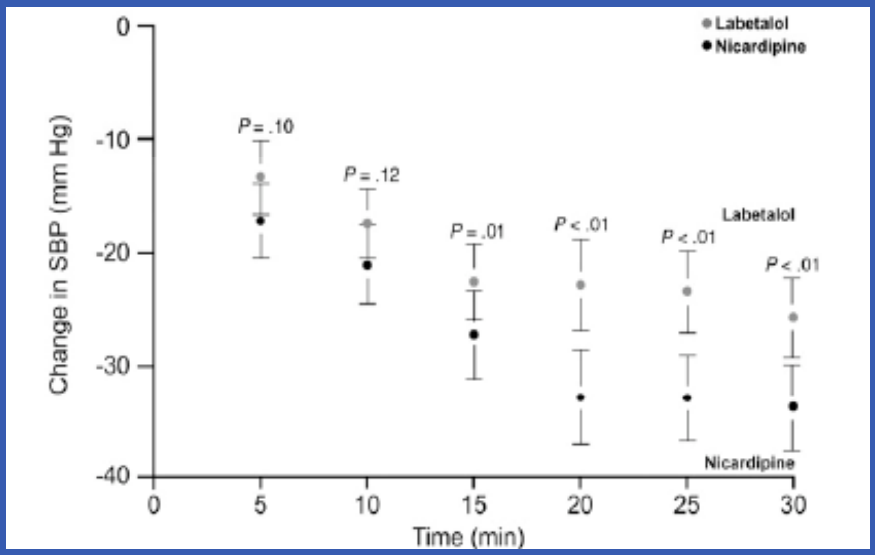
Peacock et al, Am J Emerg Med, 2012

24 hour BP Control



Peacock et al, Am J Emerg Med, 2012

Acute BP Control



Peacock et al, Am J Emerg Med, 2012

Acute BP Control in ICH

- Numerous studies
  - ATACH, INTERACT, others
- Many used IV Nicardipine for acute control
- Were able to achieve SBPs < 180 and around 140 in some studies
- Trend towards less hematoma growth in some studies
- SAFE TO DO SO; no evidence of clinical harm
- No obvious clinical benefits
  - WHY?
  - Selected patients who had small/medium sized bleeds
  - These patients were destined to do well with either therapy

Conclusions

- Lowering of BP in most patients with AIS seems to offer no firm or consistent benefit in most cases
  - But long term Rx of HTN is extremely important
- Lowering of BP in patients with ICH appears to be safe, especially with IV Nicardipine; clinical benefit remains to be confirmed
- Long terms Rx of HTN remains of immense public health concern

Policy Implications

- Should treatment of HTN be a treatment standard or performance metric for all stroke patients with HTN?
- Might have major public health implications
- Currently is not part of being a PSC or CSC
- Is this tracked in PCP practices?
  - Should it be??