İNME SONRASINDA HİPERTANSİYON TEDAVİSİ

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Erciyes Üniversitesi Tıp Fakültesi

Nefroloji Bilim Dalı

- Yıllık 15 milyon insan inme geçiriyor;

  1/3 mortalite

  1/3 kalıcı sakatlık
- İnme geçiren hastalarda tekrarlayıcı inme riski oldukça yüksek (5 yıl içinde 1/6 yeni atak)
- Koroner ve periferik arterlerde iskemik olay riski de yüksek
- Tekrarlayan inmenin ve diğer iskemik olayların önlenmesi için etkin ve güvenilir tedaviler öncelik taşıyor; HT tedavisi en önde gelen yaklaşımlardan birisi

Brown DL et al. Stroke 2005;36:1285–1287.

İNME ve HİPERTANSİYON (KAN BASINCI)

*HT serebrovasküler olaylar için en önemli modifiye edilebilir risk faktörüdür
*Sistolik kan basıncı ile ilişki diyastolik kan basıncından daha güçlüdür
*İlk iskemik inme için risk, SKB'nin 115 mmHg kadar düşük düzeylerinden başlayarak KB ile doğrudan ilişkilidir; SKB'de her bir mmHg artış riski de artırır
*Tekrarlayan inme için de bu ilişki olasılıkla benzerdir
*Kan basıncı hem hipertansif hem de non-hipertansif bireylerde inme riski için önemli bir belirleyicidir

Lewington S, et al. Lancet 2002;360:1903-13.
Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Lancet 1998;352:1801-07.

Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials

Methods We did seven sets of prospectively-designed overviews with data from 29 randomised trials (n=162 341). The trial eligibility criteria, primary outcomes, and main hypotheses were specified before the result of any contributing trial was known.

YORUM

Kan basıncını düşürücü tedavi, inmede dahil toplam kardiyovasküler olay riskini düşürür ve kan basıncında daha büyük düşüşler riskte de daha büyük azalma sağlar

β blockers, although ACE-inhibitor-based regimens reduced blood pressure less. There was evidence of some differences between active regimens in their effects on cause-specific outcomes. For every outcome other than heart failure, the difference between randomised groups in achieved blood pressure reduction was directly related to the observed difference in risk.

Interpretation Treatment with any commonly-used regimen reduces the risk of total major cardiovascular events, and larger reductions in blood pressure produce larger reductions in risk.

Turnbull F et al. Lancet. 2003;362:1527-35.

İNME ve HİPERTANSİYON

- İskemik inmenin sekonder koruması için olasılıkla en önemli önlem «hipertansiyon tedavisi»
- Yakın zamanda meydana gelmiş iskemik inmeli hastalarda HT prevalansı %70
- Serebral hemoraji öyküsü olanlarda «kan basıncını düşürücü tedavi dışında» kanıtlanmış sekonder koruma seçeneği mevcut değil

Lovett JK et al. Neurology. 2004;62:569-73.
Lawes CM et al. Stroke. 2004;35:776-85.

Chin Med J (Engl). 1995 Sep;108(9):710-7.

Post-stroke antihypertensive treatment study. A preliminary result.

PATS Collaborating Group.

- İnmeden sekonder korunma için HT tedavisinin etkinliğini gösteren **ilk randomize kontrollü prospektif çalışma**
- 5665 GİA veya inmeli (iskemik veya hemorajik) hasta (ortalama yaş: 60); indapamid 2.5 mg (2840) ve plasebo (2825) kollarına randomize ediliyor
- İnme ile randomizasyon arası zaman 31 ay
- Primer sonlanım noktası «tekrarlayan inme»
- Ortalama 2 yıl takip
- Bazal ortalama KB: 154/94 mmHg
- Yaklaşık %84 hipertansif
- Aktif kolda KB 6.8/3.3 mmHg daha fazla düşmüş

PATS Collaborating Group. Chin Med J (Engl). 1995;108:710-7.

	İndapamid grubu, n: 2825	Plasebo grubu, n: 2840	HR (%95 GA)	*P*
Tekrarlayan inme	**143**	**219**	**0.69 (0.54-0.89)**	**<0.001**
Kardiyovasküler olay	**199**	**258**	**0.75 (0.62-0.89)**	**0.002**

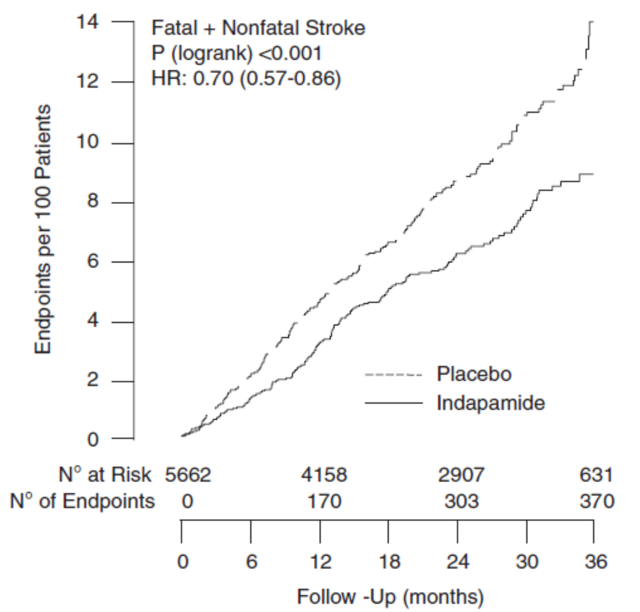


Figure 3 Cumulative incidence of fatal and nonfatal stroke recurrence by treatment group in the Post-stroke Antihypertensive Treatment Study.

Table 4 Subgroup analysis of fatal combined with nonfatal stroke

Baseline characteristic	*Rate per 1000 patient-years (no. of strokes/no. of patients at risk)* Placebo (n=2825)	Indapamide (n=2840)	*Difference*[a] *% Rate (95% CI)*	P_{int}
Women	42.3 (56/785)	26.1 (36/803)	−38 (−59 to −6)	0.49
Men	44.7 (163/2040)	32.6 (123/2037)	−27 (−42 to −8)	
<60 years	35.6 (91/1395)	26.3 (71/1434)	−26 (−47 to −1)	0.72
⩾60 years	53.1 (128/1430)	35.9 (88/1406)	−32 (−48 to −11)	
Normotension[b]	34.5 (28/470)	17.2 (13/443)	−50 (−74 to −4)	0.30
Hypertension	46.0 (191/2355)	33.2 (146/2397)	−28 (−42 to −10)	
Hemorrhagic stroke[c]	40.0 (29/404)	36.8 (28/410)	−8 (−45 to 55)	0.28
Thromboembolic stroke	44.4 (185/2118)	30.2 (130/2127)	−32 (−46 to −15)	
<6 months[d]	47.8 (82/931)	32.3 (57/923)	−32 (−52 to −8)	0.74
⩾6 months	41.5 (133/1584)	30.3 (100/1599)	−48 (−59 to −5)	

PATS Collaborating Group. Chin Med J (Engl). 1995;108:710-7.

Articles

PROGRESS (perindopril protection against recurrent stroke study)

Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack

*PROGRESS Collaborative Group**

- **Amaç:** İnme (iskemik veya hemorajik) veya GİA öyküsü olan hastalarda kan basıncını düşürücü rejimin etkisini belirlemek
- 6105 hasta (ortalama yaş: 64) randomize ediliyor; aktif tedavi kolu (3051)/ plasebo kolu (3054)
- Aktif tedavi kolu; 4 mg perindopril veya 4 mg perindopril + 2.5 mg indapamid
- Primer sonlanım noktası «fatal veya non-fatal inme»
- Yaklaşık 4 yıllık takip süresi
- Bazal ortalama KB: 147/86 mmHg
- Yarısı hipertansif (159/94 mmHg), diğer yarısı hipertansif değil (136/79 mmHg)
- Aktif kolda KB 9/4 mmHg daha↓ (Kombine kolda 12/5 mmHg; sadece perindopril kolunda 5/3 mmHg)

PROGRESS Collaborative Group. Lancet. 2001;358:1033-41

Primer sonlanım noktası %10 vs. %14

	Number of events: Active (n=3051)	Number of events: Placebo (n=3054)	Relative risk reduction (95% CI)
Stroke subtypes			
Fatal or disabling	123	181	33% (15 to 46)
Not fatal or disabling	201	262	24% (9 to 37)
Ischaemic stroke	246	319	24% (10 to 35)
Cerebral haemorrhage	37	74	50% (26 to 67)
Stroke type unknown	42	51	18% (–24 to 45)
Total stroke	**307**	**420**	**28% (17 to 38)**
Major vascular events			
Vascular death	181	198	9% (–12 to 25)
Non-fatal MI	60	96	38% (14 to 15)
Non-fatal stroke	275	380	29% (17 to 39)
Total events	**458**	**604**	**26% (16 to 34)**
Mortality			
Stroke	42	50	16% (–27 to 44)
Coronary	58	62	7% (–34 to 39)
Other vascular	81	86	6% (–28 to 30)
Cancer	64	65	2% (–39 to 30)
Other non-vascular	61	56	–9% (–57 to 24)
Total deaths	**306**	**319**	**4% (–12 to 18)**

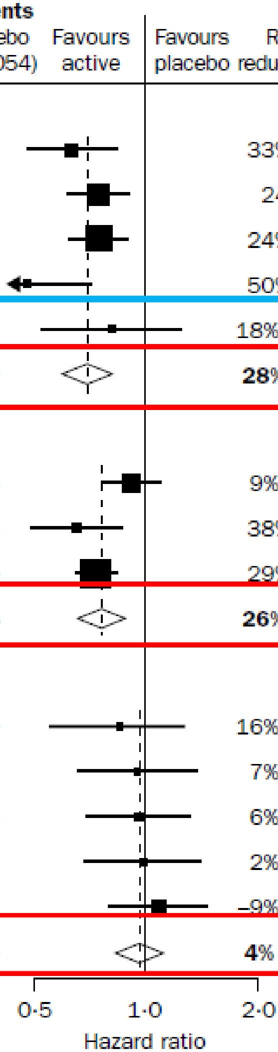


Figure 4: **Effects of study treatment on stroke subtypes, major vascular events, and deaths**
Black squares=point estimates (with area proportional to number of events); horizontal lines=95% CIs. Diamonds=point estimate and 95% CI for overall effects. Vertical broken line=point estimate for overall effect. MI=myocardial infarction.

	Events/patients: Active	Events/patients: Placebo	Relative risk reduction (95% CI)
Stroke			
Combination	150/1770	255/1774	43% (30 to 54)
Single drug	157/1281	165/1280	5% (–19 to 23)
Hypertensive	163/1464	235/1452	32% (17 to 44)
Non-hypertensive	144/1587	185/1602	27% (8 to 42)
Total stroke	**307/3051**	**420/3054**	**28% (17 to 38)**
Major vascular events			
Combination	231/1770	367/1774	40% (29 to 49)
Single drug	227/1281	237/1280	4% (–15 to 20)
Hypertensive	240/1464	331/1452	29% (16 to 40)
Non-hypertensive	218/1587	273/1602	24% (9 to 37)
Total events	**458/3051**	**604/3054**	**26% (16 to 34)**

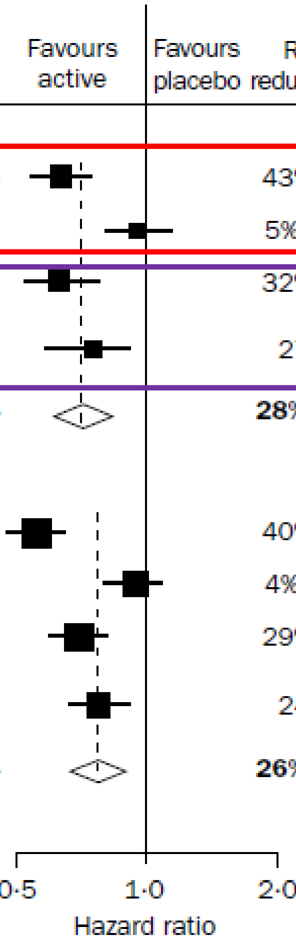


Figure 5: **Effects of study treatment on stroke and major vascular events in subgroups of patients**
Hazard ratios (and 95% CIs) for hypertensive and non-hypertensive subgroups standardised to study-wide proportions of patients for whom combination or single drug therapy was planned. p values for homogeneity (combination therapy *vs* single drug therapy) both <0·001. p values for homogeneity (hypertensive *vs* non-hypertensive) both >0·6. Conventions as in figure 4.

PROGRESS Collaborative Group. Lancet. 2001;358:1033-41

Interpretation This blood-pressure-lowering regimen reduced the risk of stroke among both hypertensive and non-hypertensive individuals with a history of stroke or transient ischaemic attack. Combination therapy with perindopril and indapamide produced larger blood pressure reductions and larger risk reductions than did single drug therapy with perindopril alone. Treatment with these two agents should now be considered routinely for patients with a history of stroke or transient ischaemic attack, irrespective of their blood pressure.

Lancet 2001; **358:** 1033–41

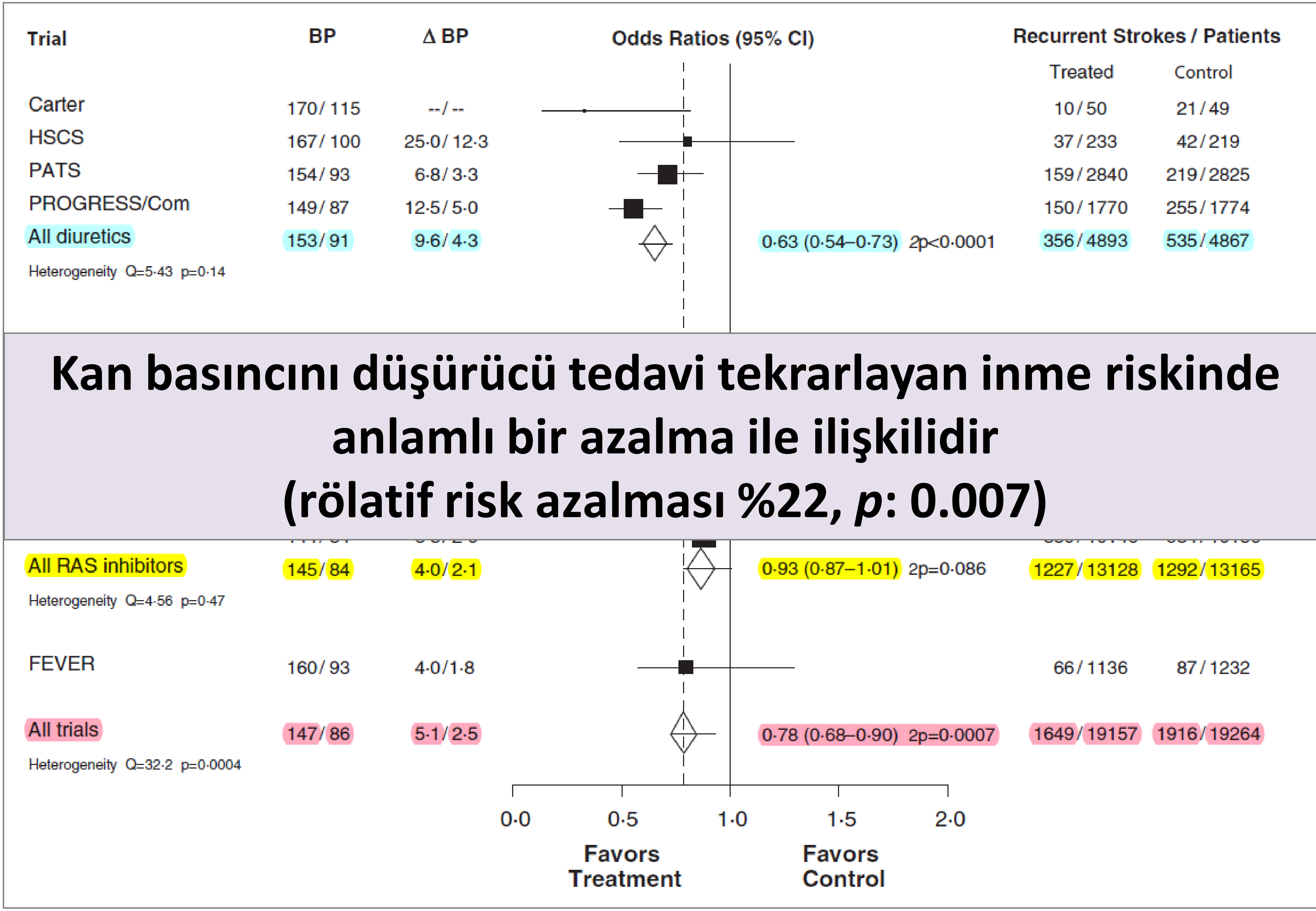
YORUM: Bu kan basıncını düşürücü rejim inme veya geçici iskemik atak öyküsü olan hem hipertansif hem de hipertansif olmayan kişilerde tekrarlayan inme riskini azaltır. Perindopril + indapamid kombinasyon tedavisi tek başına perindopril tedavisinden daha fazla kan basıncı düşüşü ve daha fazla risk azalması sağlar. **Bu iki ajanla tedavi inme veya geçici iskemik atak öyküsü olan hastalar için kan basınçlarına bakılmaksızın rutin olarak düşünülmelidir.**

Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature

Characteristics of trials and of patients with previous cerebrovascular event

	Carter	*HSCS*	*Dutch TIA*	*TEST*	*PROGRESS*	*HOPE*[a]	*SCOPE*[a]	*FEVER*[a]	*PRoFESS*
References	3	4	5	6	7,11	8,12	9,13	10	1
Year of publication	1970	1993	1993	1995	2001	2002	2003	2005	2009
Design									
Degree of blinding	None	Double	Double	Double	Double	Double	Double	Double	Double
Reference/intervention	49/50	219/233	741/732	348/372	3054/3051[b]	513/500	97/97	1232/1136	10 186/10 146
Study medication									
Reference (daily dose in mg)	No treatment	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo[c]	HCTZ (12.5) plus placebo	Placebo
Intervention (daily dose in mg)	Thiazides, α-methyldopa (250–2000), bethanidine (10–200), debrisoquine (10–200)	Deserpide (0.5–1.0) plus methylclothiazide (5–10)	Atenol (50)	Atenolol (50)	Perindopril (4) plus/minus indapamide (2.0–2.5)	Ramipril (2.5–10.0)	Candesartan[c] (8–16)	HCTZ (12.5) plus felodipine (5.0)	Telmisartan (80)
Mean characteristics									
Age, years	64.1	59.0	70.9	70.4	64.0	66.0	76.4	61.5	66.0
SBP/DBP, mm Hg	170/115[d]	167/100	157/91	161/88	147/86	139/79	166/90	160/93	144/84
Body mass index (kgm^{-2})	—	—	—	—	—	28.0	27.0	26.3	26.8
Proportion of patients									
Women	43.3	41.4	70.9	39.8	30.3	26.7	64.5	39.0	36.0
White	100.0	19.5	100.0	100.0	61.5	~100.0	100.0	0	
Black	0	80.5	0	0	0	—	0	0	
Asian	0	0	—	0	38.5	—	0	100.0	
Hypertension at entry[e] (treated)	100.0 (50.5)	100.0 (0)	4.8 (—)	100.0 (—)	64.0 (50.0)	46.8 (100.0)	100.0 (52.7)	100.0 (100.0)	74.0 (—)
Smokers	—	58.6	7.9	23.4	20.0	14.2	8.7	29.1	21.2
Myocardial infarction	—	—	0.9	10.0	0.1	52.6	4.5	1.9	6.7
Diabetes mellitus	—	35.8	0.8	12.5	12.5	38.5	12.1	12.8	28.2
Average follow-up (years)	4.0	3.0	2.6	2.6	3.9	5.0	3.7	3.3	2.5

Liu L, et al. Hypertens Res. 2009 ;32:1032-40



Kan basıncını düşürücü tedavi tekrarlayan inme riskinde anlamlı bir azalma ile ilişkilidir (rölatif risk azalması %22, *p*: 0.007)

Liu L, et al. Hypertens Res. 2009 ;32:1032-40

Blood Pressure Reduction and Secondary Prevention of Stroke and Other Vascular Events

A Systematic Review

Parveen Rashid, MRCP(UK); Jo Leonardi-Bee, MSc; Philip Bath, MD, FRCP

Effect of lowering blood pressure on stroke, myocardial infarction, all vascular events, and death

Outcome	Trials	Events	Subjects	Rate in Control Group, %	OR	95% CI	*P*	Heterogeneity, *P*
Stroke, all	7	1577	15 527	11.5	**0.76**	**0.63–0.92**	**0.005**	**0.01**
Stroke, fatal	7	329	15 527	2.4	0.76	0.56–1.03	0.08	0.16
Stroke, nonfatal	7	1268	15 527	9.2	**0.79**	**0.65–0.95**	**0.01**	**0.042**
Myocardial infarction, all	6	555	15 428	4.0	**0.79**	**0.63–0.98**	**0.03**	**0.19**
Vascular events, all	6	2225	15 428	16.0	**0.79**	**0.66–0.95**	**0.01**	**0.002**
Death, vascular	7	852	15 527	5.9	0.86	0.70–1.06	0.16	0.066
Death, all	7	1427	15 527	9.6	0.91	0.79–1.05	0.18	0.17

Antihipertansif tedavi aynı zamanda MI ve tüm kardiyovasküler olay riskini de azaltmaktadır

Rashid P, et al. Stroke. 2003;34:2741-8.

İNMELİ HASTADA ANTİHİPERTANSİF TEDAVİ İLE AMAÇLANAN

- İnmenin tekrarını (rekürrens) önlemek
- Diğer kardiyovasküler komplikasyonları önlemek

İNMELİ HASTADA ANTİHİPERTANSİF TEDAVİ

- HANGİ HASTALARI TEDAVİ EDELİM?
- TEDAVİYE NE ZAMAN BAŞLAYALIM?
- HANGİ İLACI BAŞLAYALIM?
- HEDEF KAN BASINCI NE OLMALI?

AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Stroke 2014;45:2160

Size of Treatment Effect

Class I: Yarar >>> Risk; Tedavi verilmelidir
Class IIa: Yarar >> Risk; Tedaviyi vermek mantıklıdır
Class IIb: Yarar ≥ Risk: Tedavi göz önünde bulundurulabilir
Class III Yararlı değil veya zararlı; Tedavi önerilmiyor

Estimate Certainty (Precision) of Treatment Effect

Level A: Bir çok popülasyonda değerlendirilmiş/çok sayıda randomize çalışma veya meta-analizden elde edilmiş veri
Level B: Kısıtlı popülasyonda değerlendirilmiş/tek randomize çalışamadan veya nonrandomize çalışmalardan elde edilmiş veri
Level C: Çok kısıtlı popülasyonda değerlendirilmiş/sadece uzmanların konsensus görüşleri, vaka çalışmalarından elde edilen veri

İNMELİ HASTADA ANTİHİPERTANSİF TEDAVİ

HANGİ HASTALARI TEDAVİ EDELİM?

TEDAVİYE NE ZAMAN BAŞLAYALIM?

HANGİ İLACI BAŞLAYALIM?

HEDEF KAN BASINCI NE OLMALI?

- ***Herhangi bir tipte iskemik inme veya GİA geçiren bir hasta;***

□ Bilinen HT olan ve daha önce tedavi edilen hastalarda antihipertansif tedavi yeniden başlanmalıdır (hem tekrarlayan inmeyi hem de diğer vasküler olayları engellemek için) (Class I; kanıt düzeyi A)**

□ Daha önce antihipertansif tedavi almayan ve SKB ≥140 mmHg veya DKB ≥90 mmHg olan hastalarda antihipertansif tedavi başlanmalıdır (Class I; kanıt düzeyi B)**

□ Daha önce antihipertansif tedavi almayan ve KB <140/90 mmHg ise, tedaviye başlamak kesin olmayan yarara sahiptir (Class IIb; kanıt düzeyi C)**

**AHA/ASA guideline,Kernan WN, et al. Stroke. 2014 ;45:2160-236

Aterotrombotik, laküner (küçük damar oklüzyonu) veya kriptojenik tip iskemik inme veya GİA’sı olan ve daha önce antihipertansif tedavi almayan hastalarda KB >120/70 mmHg ise antihipertansif tedavinin başlanması öneriliyor (ZAYIF BİR ÖNERİ)*

*Kaplan NM, Uptodate 2015

HANGİ HASTALARA TEDAVİ BAŞLAMAYALIM

- Kardiyoembolik fenomen (AF) veya paradoksal emboli nedeniyle GİA veya inmesi olan nonhipertansif (KB <140/90 mmHg) hastalar*
- Bazal kan basıncı <120/70 mmHg olan tüm hastalar*

*Kaplan NM, Uptodate 2015

İNMELİ HASTADA ANTİHİPERTANSİF TEDAVİ

HANGİ HASTALARI TEDAVİ EDELİM?

TEDAVİYE NE ZAMAN BAŞLAYALIM?

HANGİ İLACI BAŞLAYALIM?

HEDEF KAN BASINCI NE OLMALI?

Hastanede tedavi edilmeyen ayaktan hastalar için, tüm uygun hastalarda antihipertansif tedavi başlanmalıdır veya daha önceden tedavi alıyorsa (ve kesilmişse) yeniden başlanmalıdır*

İnme stabilize olduktan sonra (ilk birkaç günden sonra), kronik faz için antihipertansif tedaviye geçilmelidir **

Daha önce hipertansiyonu olan ve nörolojik olarak stabil hastalarda ilk 24 saatten sonra antihipertansif tedaviye tekrar başlanabilir***

*Kaplan NM, Uptodate 2015

**AHA/ASA guideline,Kernan WN, et al. Stroke. 2014 ;45:2160-236

***Jauch EC, et al. Stroke. 2013;44:870–947.

İNMELİ HASTADA ANTİHİPERTANSİF TEDAVİ

HANGİ HASTALARI TEDAVİ EDELİM?

TEDAVİYE NE ZAMAN BAŞLAYALIM?

HANGİ İLACI BAŞLAYALIM?

HEDEF KAN BASINCI NE OLMALI?

- İlaç sınıfları arasında doğrudan karşılaştırmaların yapıldığı çalışma sayısı kısıtlı olduğu için, önerilen kan basıncındaki düşüşlere ulaşmak için optimal bir ilaç rejimi seçimi belirsizdir**

PATS Çalışması: İndapamid ile tekrarlayan inme riskinde %31 bir azalma

PROGRESS Çalışması: Tekrarlayan inme riskinde «perindopril + indapamid» kombine tedavisi ile %43 azalma ama «sadece perindopril» ile %5 (anlamsız) azalma

**AHA/ASA guideline,Kernan WN, et al. Stroke. 2014 ;45:2160-236

NIH Public Access
Author Manuscript
N Engl J Med. Author manuscript; available in PMC 2009 July 22.

ProFESS Study

Published in final edited form as:
N Engl J Med. 2008 September 18; 359(12): 1225–1237. doi:10.1056/NEJMoa0804593.

Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events

- **Amaç; iskemik inmeden sonra erken dönemde (inme sonrası 15 gün) başlanan telmisartanın etkinliğini değerlendirmek**
- İskemik inmeli 20332 hasta (ortalama yaş: 66); telmisartan (80 mg) veya plaseboya randomize ediliyor
- ARB dışında diğer tüm antihipertansif ilaçlara ek tedavi olarak izin veriliyor
- **Primer sonlanım noktası «tekrarlayan inme»**
- Ortalama 2.5 yıl takip
- Bazal ortalama KB: 144/84 mmHg
- Yaklaşık %74 hipertansif
- Aktif kolda KB plaseboya kıyasla 3.8/2 mmHg↓

Yusuf S, et al. N Engl J Med. 2008;359:1225-37

Klinik sonuç	Telmisartan, n: 10146	Plasebo, n: 10186	HR (%95 GA)	*P*
Primer				
Tekrarlayan inme	**880 (8.7)**	**934 (9.2)**	**0.95 (0.86-1.04)**	**0.23**
İskemik	**774 (7.6)**	**811 (8.0)**		
bilinmeyen				
Sekonder				
Kardiyovasküler nedenlerden, tekrarlayan inme, MI veya KY kaynaklı ölüm	**1367 (13.5)**	**1463 (14.4)**	**0.94 (0.87-1.01)**	**0.11**

İskemik inmeden hemen sonra başlanan telmisartan tedavisi tekrarlayan inme, majör kardiyovasküler olay ve diyabet gelişme riskini anlamlı olarak azaltmıyor

Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention

Principal Results of a Prospective Randomized Controlled Study (MOSES)

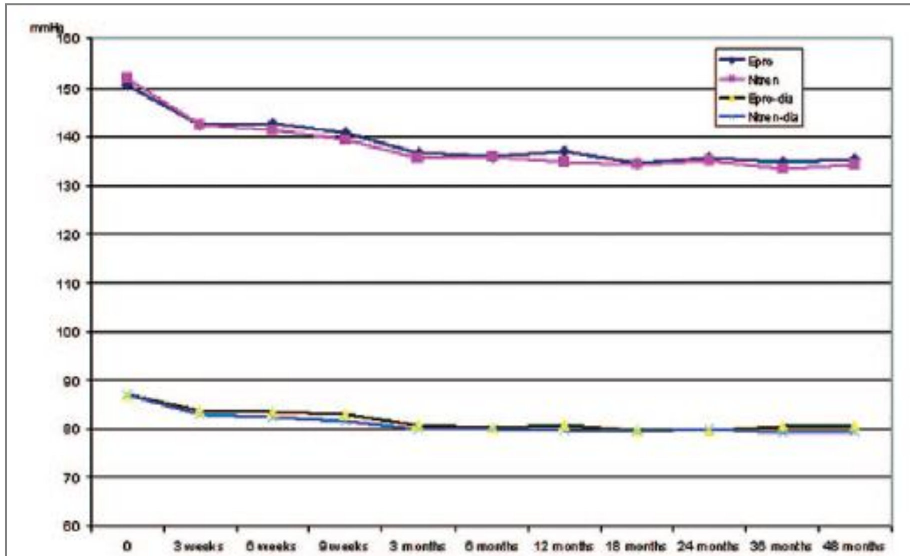
Joachim Schrader, MD; Stephan Lüders, MD; Anke Kulschewski, MD; Frank Hammersen, MD; Kerstin Plate;
Jürgen Berger, PhD; Walter Zidek, MD; Peter Dominiak, MD; Hans Christoph Diener, MD;
for the MOSES Study Group

Background and Purpose—In hypertensive stroke patients, for the same level of blood pressure control, eprosartan will be more effective than nitrendipine in reducing cerebrovascular and cardiovascular morbidity and mortality.

TABLE 1. Baseline Characteristics of Patients

	Eprosartan	Nitrendipine
Total No. of eligible patients	681	671
Sex, No. (%, male)	365 (53.6)	368 (54.8)
Age, y	67.7±10.4	68.1±9.5
Body mass index	27.7±4.2	27.4±4.4
Time between qualifying event and allocation, days	347.6±322.5	349.8±325.7
Patients enrolled within 1 week of qualifying event	20 (2.9)	21 (3.1)
Systolic office blood pressure, mm Hg	150.7±18.5	152.0±18.2
Diastolic office blood pressure, mm Hg	87.0±10.8	87.2±9.6
Heart rate, bpm	74.7±10.2	75.7±10.5
Mean systolic 24-hour blood pressure, mm Hg	139.7±16.9	140.0±16.9
Mean diastolic 24-hour blood pressure, mm Hg	81.7±10.9	81.5±10.9
Mean systolic daytime blood pressure, mm Hg	143.1±17.6	143.9±19.0
Mean diastolic daytime blood pressure, mm Hg	84.0±12.0	84.3±12.6
Mean systolic night blood pressure, mm Hg	132.1±20.1	132.1±19.8
Mean diastolic night blood pressure, mm Hg	75.8±11.9	75.6±12.0
Qualifying disease		
Stroke	418 (61.4)	407 (60.7)
TIA	186 (27.3)	184 (27.4)
PRIND	36 (5.3)	47 (7.0)
Intracerebral hemorrhage	41 (6.0)	33 (4.9)

Primer sonlanım noktası: tüm nedenlere bağlı mortalite ve kardiyovasküler ve serebrovasküler olaylar (bileşik sonlanım noktası)



Results—Randomization was successful without significant differences in the baseline characteristics. Blood pressure was reduced to a comparable extent without any significant differences between the 2 groups during the whole study period (150.7/84 mm Hg and 152.0/87.2 mm Hg with eprosartan and nitrendipine therapy to 137.5/80.8 mm Hg and 136.0/80.2 mm Hg, respectively, confirmed by ambulatory blood pressure monitoring). Moreover, already after 3 months, normotensive mean values were achieved, and 75.5% reached values <140/90 mm Hg with the eprosartan regimen and 77.7% with the nitrendipine regimen. During follow-up, in total, 461 primary events occurred: 206 eprosartan and 255 nitrendipine (incidence density ratio [IDR], 0.79; 95% CI, 0.66 to 0.96; P=0.014). Cardiovascular events were: 77 eprosartan and 101 nitrendipine (IDR, 0.75; 95% CI, 0.55 to 1.02; P=0.06); cerebrovascular events: 102 eprosartan and134 nitrendipine (IDR, 0.75; 95% CI, 0.58 to 0.97; P=0.03).

TABLE 3. End Point Analysis (total occurrence in each category, including recurrent events)

		Eprosartan		Nitrendipine					
	Total	No.	ID	No.	ID	IDR	95% CI		*P*
Primary combined endpoint: cerebrovascular and cardiovascular events and noncardiovascular death	461	206	13.25	255	16.71	0.79	0.66	0.96	0.014
Fatal and nonfatal cardiovascular	178	77	4.95	101	6.62	0.75	0.55	1.02	0.061
Fatal and nonfatal cerebrovascular	236	102	6.56	134	8.78	0.75	0.58	0.97	0.026

Total patient years: eprosartan 1554.69; nitrendipine 1515.27.
ID indicates incidence density per 100 person years; IDR, $ID_{Eprosartan}/ID_{Nitrendipin}$; 95% CI, 95% CI of IDR.

Conclusions—The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study was the first to compare an angiotensin II type 1 receptor antagonist with a calcium antagonist in secondary stroke prevention. In these high-risk hypertensive stroke patients, an early normotensive and comparable blood pressure was achieved. The combined primary end point was significantly lower in the eprosartan group. (*Stroke*. **2005;36:1218-1226.**)

Controversies in Stroke

Section Editors: Geoffrey A. Donnan, MD, FRACP, and
Stephen M. Davis, MD, FRACP

Angiotensin Receptor Blockers Should Be Regarded as First-Line Drugs for Stroke Prevention in Both Primary and Secondary Prevention Settings

Yes

Daniel G. Hackam, MD, PhD, FRCPC

Angiotensin Receptor Blockers Should Be Regarded as First-Line Drugs for Stroke Prevention in Both Primary and Secondary Prevention Settings

No

Martin H. Strauss, MD, FRCP(C), FACC; Alistair Hall, MB, ChB, PhD, FRCP(UK)

Stroke. 2009;40:3159-3160

Renin–Angiotensin System Modulators Modestly Reduce Vascular Risk in Persons With Prior Stroke

Meng Lee, MD; Jeffrey L. Saver, MD; Keun-Sik Hong, MD, PhD; Qing Hao, MD, PhD; Jessica Chow, MPH; Bruce Ovbiagele, MD, MSc

	Pre-Existing Condition in Original Trials	Active/Comparator	Patient No.	Mean Age, Y	Time From Stroke to Trial, Mo	Follow-Up Duration, Y	Baseline BP, mm Hg	Difference in BP at Trial End,* mm Hg	Jadad Score, 5-Point Maximum
CASE-J[19]	High-risk hypertension	Candesartan/amlodipine	473	63.9	>6	3.2	163/92	−1.7/−0.6	3
HOPE[20,21,26]	Vascular disease or DM plus one CV risk factor	Ramipril/placebo	1013	66.0	>2	5	151/79	10.0/4.0	5
LIFE[10,22]	Hypertension with LVH	Losartan/atenolol	728	66.9	>6	4.8	174/98	1.3/−0.4	4
MOSES[17]	Hypertension with prior stroke or TIA	Eprosartan/nitrendipine	1352	67.9	≤24	2.5	151/87	−1.5/−0.6	3
PRoFESS[15]	Ischemic stroke	Telmisartan/placebo	20 332	66.2	≤4	2.5	144/84	3.0/1.6	5
PROGRESS[16,18]	Stroke	Perindopril/placebo	2561	64.0	≤60	3.9	144/84	4.9/2.8	5
SCOPE[23]	Aged hypertensive people	Candesartan+other antihypertensive drug/placebo+other antihypertensive drug	194	76.4	NR	3.7	166/90	−0.3/1.5	5
VALUE[24,25]	CV disease or high risk hypertensive people	Valsartan/amlodipine	3014	67.3	≥3	4.2	155/88	−2.8/−1.6	5

Table 2. Effect of ACE Inhibitors or ARBs on Primary and Secondary End Points in People With a Stroke History

	ACE Inhibitors or ARBs, No./No. (%)	Comparators, No./No. (%)	RR (95% CI)	*P*
Major vascular events[15–17,19–21,23–25]	2074/14 466 (14.3)	2270/14 473 (15.7)	0.91 (0.87–0.97)	0.001
Recurrent stroke[10,15–17,19–25]	1328/14 835 (9.0)	1434/14 832 (9.7)	0.93 (0.86–0.99)	0.03
Major coronary events[15–17,20,21,24,25]	503/14 121 (3.6)	557/14 151 (3.9)	0.90 (0.80–1.01)	0.08
Total death[15,17]	812/10 827 (7.5)	792/10 857 (7.3)	1.03 (0.94–1.13)	0.57
Death from cardiovascular causes[15]	223/10 146 (2.2)	263/10 186 (2.6)	0.85 (0.71–1.02)	0.07
Hypotension[15,17]	481/10 827 (4.4)	257/10 857 (2.4)	1.87 (1.61–2.17)	<0.001

Conclusions—Treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker has a clear but rather modest effect on reducing vascular risk in persons with prior stroke. (*Stroke*. **2012;43:113-119.**)

İnmeli hastalarda ACE inhibitörü veya ARB kullanımı majör vasküler olaylar ve tekrarlayan inme riskini azaltır

Lee M, et al. Stroke. 2012;43:113-9.

OPEN ACCESS Freely available online

PLOS | ONE

The Effects of Calcium Channel Blockers in the Prevention of Stroke in Adults with Hypertension: A Meta-Analysis of Data from 273,543 Participants in 31 Randomized Controlled Trials

Gui Jv Chen, Mao Sheng Yang*

Laboratory of Disorder Genes and Department of Pharmacology, College of Pharmacy, Chongqing Medical University, Chongqing, People's Republic of China

Abstract

Background: Hypertension is a major risk factor for the development of stroke. It is well known that lowering blood pressure decreases the risk of stroke in people with moderate to severe hypertension. However, the specific effects of calcium channel blockers (CCBs) against stroke in patients with hypertension as compared to no treatment and other antihypertensive drug classes are not known.

Methods and Findings: This systematic review and meta-analysis of randomized controlled trials (RCTs) evaluated CCBs effect on stroke in patients with hypertension in studies of CCBs versus placebo, angiotensin-converting-enzyme inhibitors (ACEIs), β-adrenergic blockers, and diuretics. The PUBMED, MEDLINE, EMBASE, OVID, CNKI, MEDCH, and WANFANG databases were searched for trials published in English or Chinese during the period January 1, 1996 to July 31, 2012. A total of 177 reports were collected, among them 31 RCTs with 273,543 participants (including 130,466 experimental subjects and 143,077 controls) met the inclusion criteria. In these trials a total of 9,550 stroke events (4,145 in experimental group and 5,405 in control group) were reported. CCBs significantly decreased the incidence of stroke compared with placebo (OR = 0.68, 95% CI 0.61–0.75, $p<1\times10^{-5}$), β-adrenergic blockers combined with diuretics (OR = 0.89, 95% CI 0.83–0.95, $p=7\times10^{-5}$) and β-adrenergic blockers (OR = 0.79, 95% CI 0.72–0.87, $p<1\times10^{-5}$), statistically significant difference was not found between CCBs and ACEIs (OR = 0.92, 95% CI 0.8–1.02, p = 0.12) or diuretics (OR = 0.95, 95% CI 0.84–1.07, p = 0.39).

Conclusion: In a pooled analysis of data of 31 RCTs measuring the effect of CCBs on stroke, CCBs reduced stroke more than placebo and β-adrenergic blockers, but were not different than ACEIs and diuretics. More head to head RCTs are warranted.

Kalsiyum kanal blokerleri (ilk) inme riskini plasebo ve beta blokerlerden daha fazla düşürür ama ACE inhibitörleri ve diüretiklerle kıyaslandığında anlamlı fark yoktur

PLoS One. 2013;8:e57854.

- Mevcut veriler diüretiklerin veya diüretik + ACEİ kombinasyonun yararlı olduğunu göstermektedir (Class I; kanıt düzeyi A)**
- Spesifik ajanların olasılıkla endike olduğu spesifik hasta özellikleri (ekstrakranyal serebrovasküler oklüziv hastalık, böbrek yetmezliği, kardiyak hastalık ve diyabet gibi) göz önünde bulundurularak tedavi seçimi bireyselleştitilmelidir (Class IIa; kanıt düzeyi B)**

**AHA/ASA guideline,Kernan WN, et al. Stroke. 2014 ;45:2160-236

- Kan basıncında yeterli bir düşüşe ulaşmak için monoterapi veya kombinasyon tedavisine mi ihtiyaç duyuluyor?
- **Monoterapi için belli bir sınıfın üstün olduğunu gösteren GÜÇLÜ BİR KANIT YOK**
- RAS blokerleri, kalsiyum kanal blokerleri, tiyazidler inmeli hastalarda başlangıç monoterapi için uygun seçenekler olabilir ama beta blokerler ilk tercih olmamalı*
- Kombinasyon tedavisi için;

  AHA/ASA kılavuzları ACE inhibitörü + bir diüretik**

  RAS blokeri + dihidropiridin kalsiyum kanal blokeri*

  (ACCOMPLISH çalışması)
- Bu ilaçlar için kontrendikasyon olmaması gerekir

*Kaplan NM, Uptodate 2015

**AHA/ASA guideline,Kernan WN, et al. Stroke. 2014 ;45:2160-236

İNMELİ HASTADA ANTİHİPERTANSİF TEDAVİ

HANGİ HASTALARI TEDAVİ EDELİM?

TEDAVİYE NE ZAMAN BAŞLAYALIM?

HANGİ İLACI BAŞLAYALIM?

HEDEF KAN BASINCI NE OLMALI?

Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

*The SPS3 Study Group**

Primer sonlanım noktası: inme (iskemik inme veya intraserebral hemoraji)

Summary

Background Lowering of blood pressure prevents stroke but optimum target levels to prevent recurrent stroke are unknown. We investigated the effects of different blood-pressure targets on the rate of recurrent stroke in patients with recent lacunar stroke.

Lancet 2013; 382: 507–15

Published Online
May 29, 2013
http://dx.doi.org/10.1016/

Hedef 130-149 mmHg

Hedef <130 mmHg

	Higher-target group (n=1519)	Lower-target group (n=1501)
Age (years)	63 (10·8)	63 (10·7)
Men	990 (65%)	912 (61%)
Blood pressure at entry (mm Hg)		
Systolic	144 (19)	142 (19)
Diastolic	79 (11)	78 (10)
Body-mass index (kg/m²)	29·2 (7·5)	29·0 (6·1)
History of hypertension	1137 (75%)	1127 (75%)
Diabetes mellitus	553 (36%)	553 (37%)
Ischaemic heart disease	173 (11%)	144 (10%)
Previous clinical stroke or TIA	211 (14%)	237 (16%)
Current tobacco smoker	308 (20%)	309 (21%)
Qualifying event		
Ischaemic stroke	1506 (99%)	1473 (98%)
TIA	13 (1%)	28 (2%)

12. ay sonunda ulaşılan ortalama sistolik kan basıncı 138 mmHg (HTG) ve 127 mmHg (LTG)

	Higher-target group (n=1519)		Lower-target group (n=1501)		Hazard ratio (95% CI)	p value
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)		
Stroke						
All stroke	152	2·77%	125	2·25%	0·81 (0·64–1·03)	0·08
Ischaemic stroke or unknown	131	2·4%	112	2·0%	0·84 (0·66–1·09)	0·19
Intracranial haemorrhage						
All	21*	0·38%	13†	0·23%	0·61 (0·31–1·22)	0·16
Intracerebral	16	0·29%	6	0·11%	0·37	0·03
					(0·68–1·04)	
Deaths						
All	101	1·74%	106	1·80%	1·03 (0·79–1·35)	0·82
Vascular death	41	0·70%	36	0·61%	0·86 (0·55–1·35)	0·52
Non-vascular	35	0·60%	40	0·68%	1·12 (0·71–1·76)	0·62
Uncertain	25	0·43%	30	0·51%	1·18 (0·69–2·00)	0·55

*One classified as both intracerebral and other, and one as both intracerebral and subdural or epidural. †One classified as intracerebral and subdural or epidural, and two as both intracerebral and other. ‡Disabling strokes classified as modified Rankin score 3 or higher after 3–6 months.

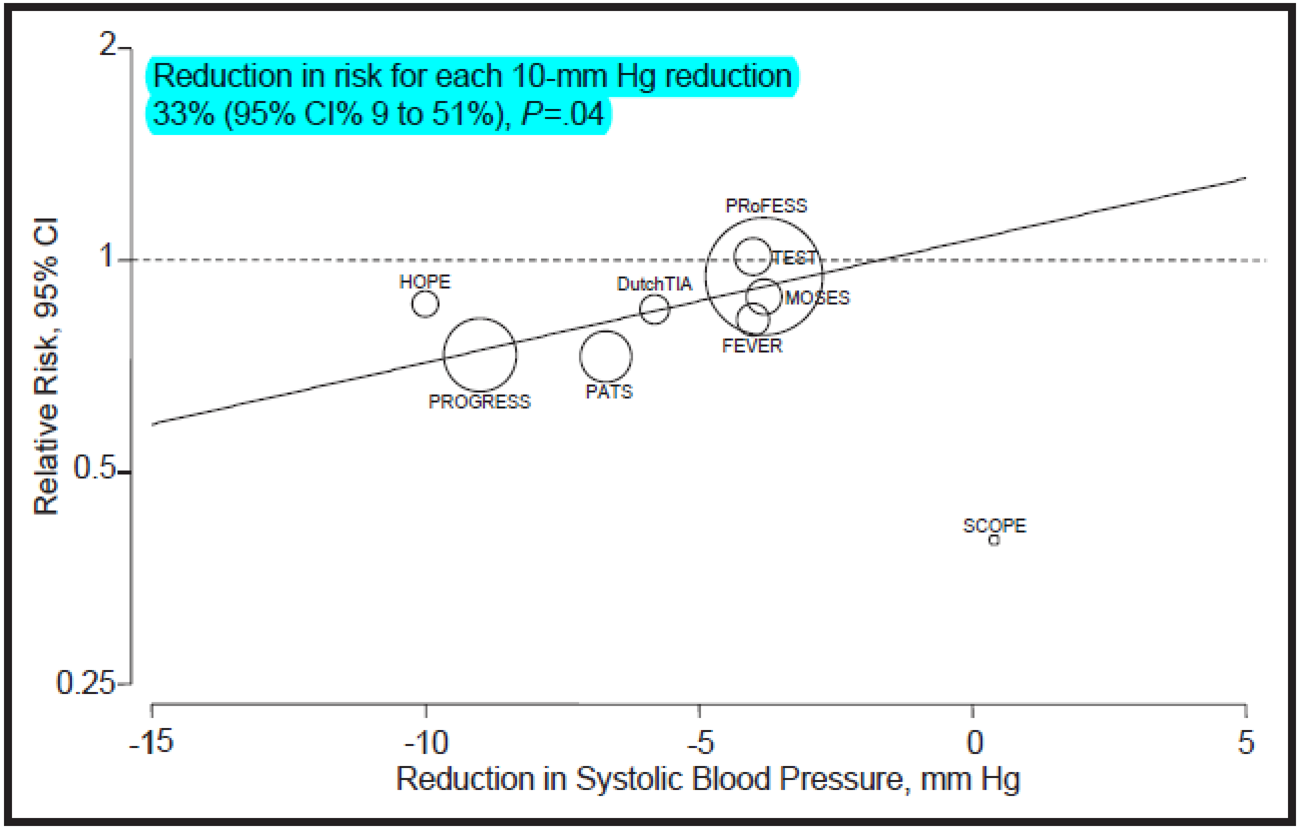
Interpretation Although … patients with recent lacunar stroke, the use o… beneficial.

İnme riskindeki azalma anlamlı olmamasına rağmen, bu sonuçlar yakın zamanda geçirilmiş laküner inmeli hastalarda 130 mmHg'den daha düşük sistolik kan basıncı hedefinin yararlı olduğunu yansıtabilir

- SPS3 ilave olarak, diğer çalışmaların bulguları da daha düşük kan basıncı değerlerinin daha iyi sonuçlar ile ilişkili olduğunu ortaya koymaktadır

- Temel kısıtlayıcı faktör bu çalışmaların hiçbirisi spesifik olarak optimal kan basıncını belirlemek için yapılmamış olması

- Ayrıca büyük servikosefalik arter stenozuna göre analizlerin olmaması da diğer bir handikap



Sistolik kan basıncında azalma ve tekrarlayan inme için risk azalması arasında ilişkiyi araştıran 9 randomize kontrollü çalışmanın meta-regresyon analizi.

***Sistolik kan basıncında her 10 mmHg azalma tekrarlayan inme riskinde %33'lük bir azalma ile ilişkilidir**

***En düşük risk; ulaşılan SKB <120 mmHg**

Arima H, et al. J Clin Hypertens. 2011;13-693-702

Blood pressure and risk of stroke in patients with cerebrovascular disease

Anthony Rodgers, Stephen MacMahon, Greg Gamble, Jim Slattery, Peter Sandercock, Charles Warlow for the United Kingdom Transient Ischaemic Attack Collaborative Group

The United Kingdom Transient Ischaemic Attack trial

- **2435 hasta (GİA, amarozis fugax veya minör inme), 4 yıllık takip**
- **Hastalar bazal KB değerlerine göre gruplara ayrılıyor;**

  DKB için ≤79, 80-89, 90-99, ≥100 mmHg

  SKB için ≤129, 130-149, 150-169, ≥170 mmHg
- **230 tekrarlayan inme**
- **Hem diyastolik hem de sistolik KB ile tekrarlayan inme gelişimi arasında lineer bir ilişki gözleniyor;**

  DKB'de her 5 mmHg↓ tekrarlayan inme riskinde %34↓

  SKB'de her 10 mmHg↓ tekrarlayan inme riskinde %28↓

Rodgers A et al. BMJ 1996;313:147.

The United Kingdom Transient Ischaemic Attack trial

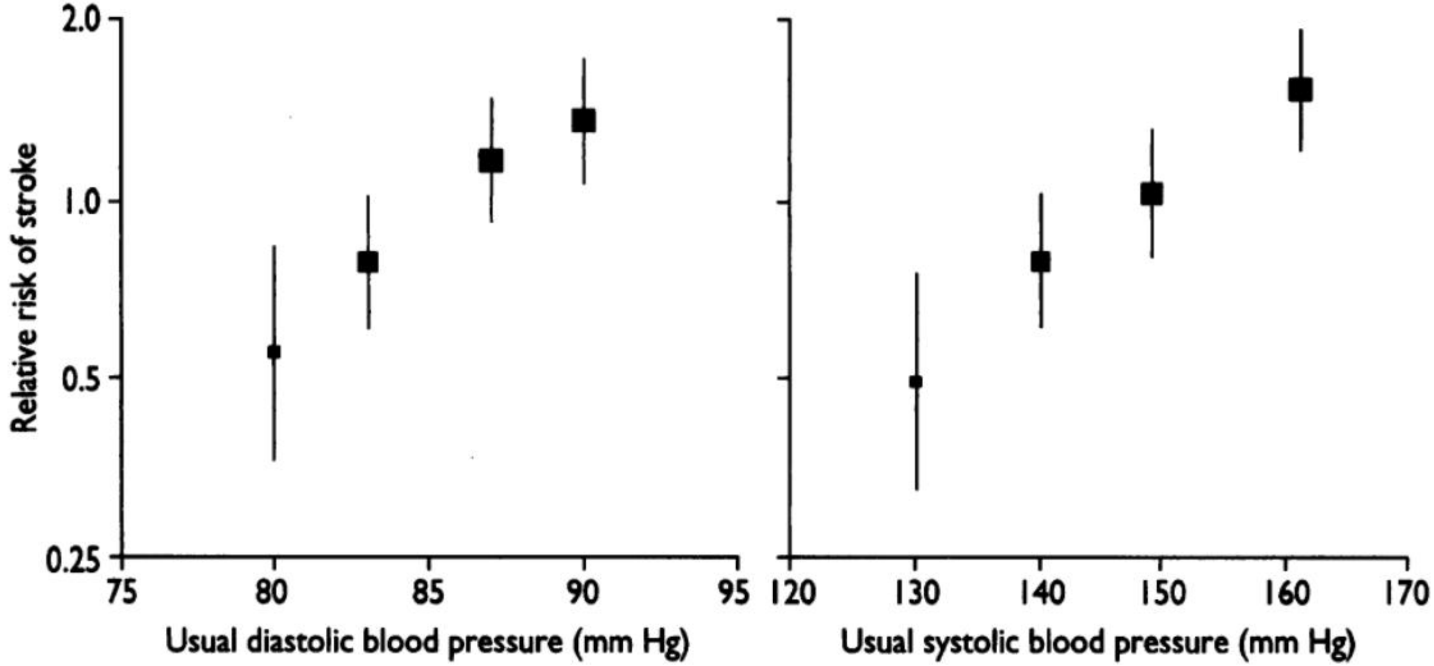
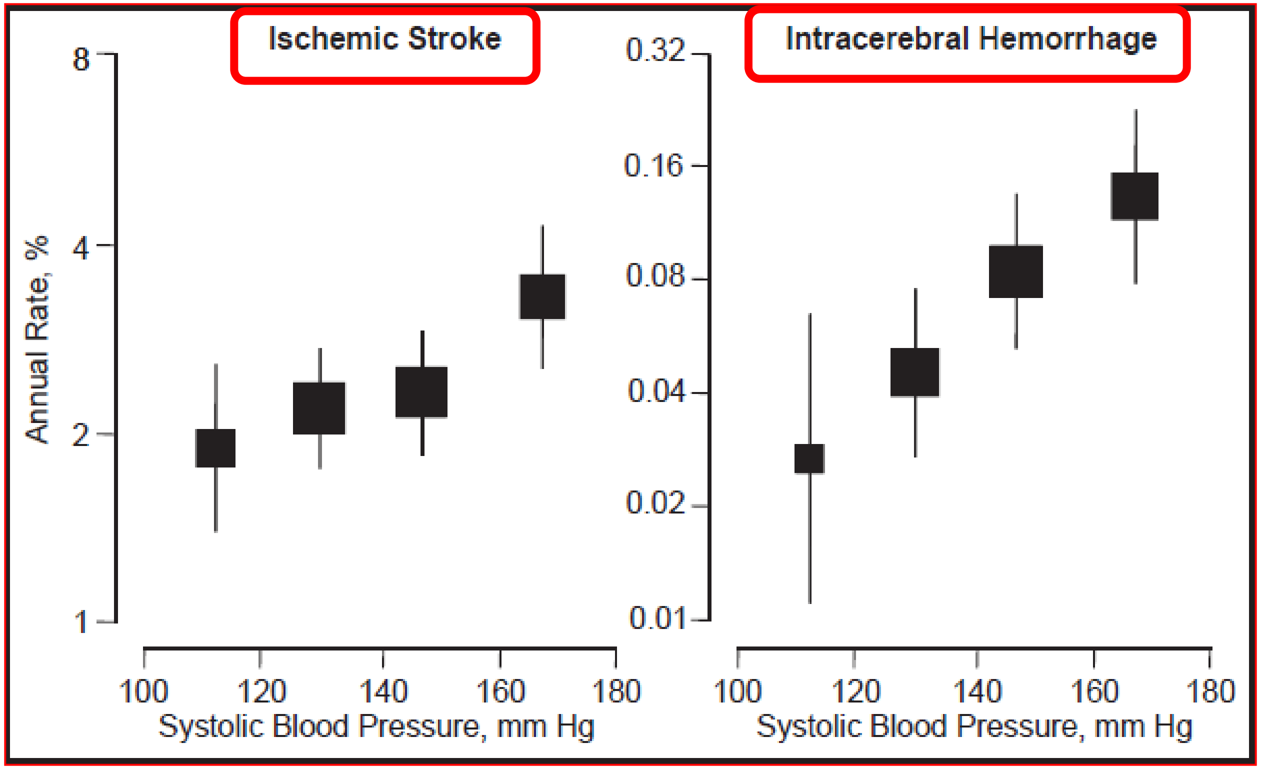


Fig 1—*Relative risk of stroke according to usual diastolic and systolic blood pressure. Vertical lines represent 95% confidence intervals, and solid squares are proportional to number of strokes in each category*

Kan basıncı düşüşü ile tekrarlayan inme riski arasında J şeklinde bir ilişki saptanmıyor

Rodgers A et al. BMJ 1996;313:147.

PROGRESS çalışması-post hoc analizi



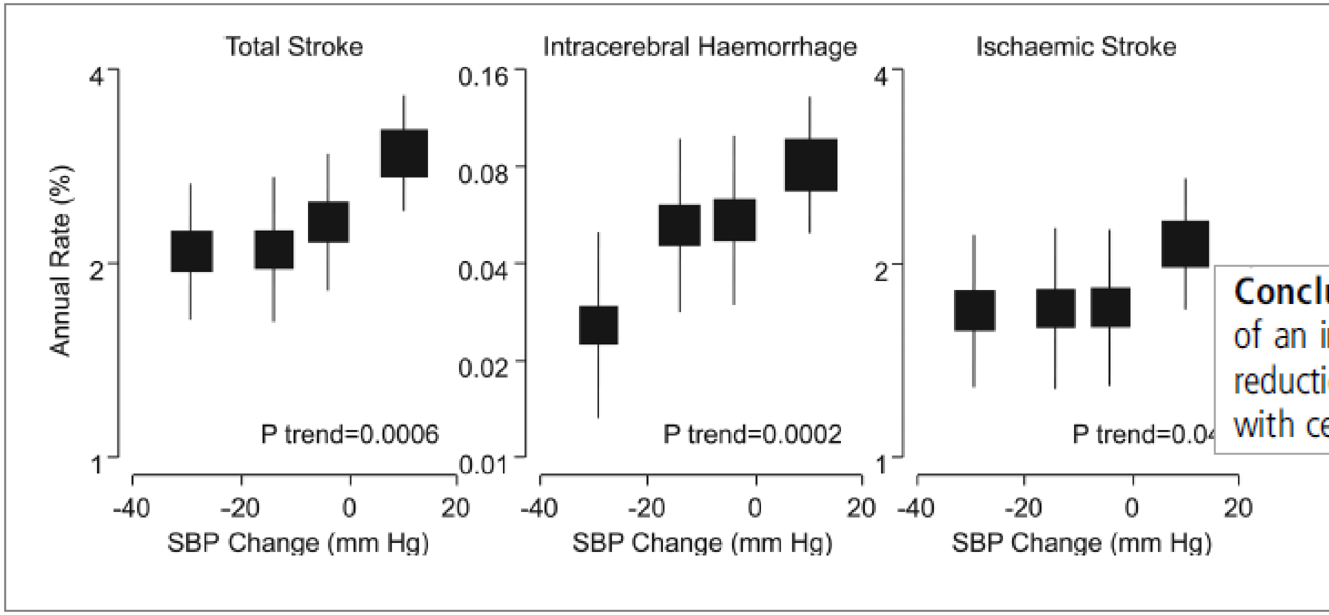
Ulaşılan SKB değerlerine göre yıllık iskemik inme ve intraserebral hemoraji oranları (*P* trend: sırasıyla 0.0005 ve <0.0001)

***Tekrarlayan inme riski ulaşılan kan basıncının en düşük olduğu grupta (112/72 mmHg) en düşükken, daha yüksek kan basınçlarında bu risk progresif olarak artmaktadır.**

***Kan basıncı ile tekrarlayan inme riski arasında J şeklinde bir ilişki saptanmıyor.**

Arima H, et al. J Hypertens 2006;24:1201-8.

PROGRESS çalışması-post hoc analizi



Conclusions The present analysis provided n
of an increase in recurrent stroke associated w
reductions in SBP produced by treatment amor
with cerebrovascular disease.

BP control in clinical practice in this high-risk group remains poor [22]. One likely reason is that clinicians remain concerned about the possible risks of cerebral hypotension and iatrogenic ischaemic stroke after BP-lowering treatment, particularly among patients with atherosclerotic cerebrovascular disease. The data presented here should allay that concern. Although the

*İnmeli hastalarda klinik pratikte KB kontrolü kötü kalmaya devam etmekte
*Olası bir nedeni klinisyenlerin özellikle aterosklerotik serebrovasküler hastalığı olan hastalarda KB düşürücü tedaviden sonra olası serebral perfüzyonun bozulması ve iyatrojenik iskemik inme riski hakkındaki endişeleridir
***Bu çalışma bu endişeyi azaltmalıdır**

Antihypertensive Treatment and Secondary Prevention of Cardiovascular Disease Events Among Persons Without Hypertension:

A Meta-analysis

Ms. Angela M. Thompson, MSPH, Mr. Tian Hu, MS, BM, Dr. Carrie L. Eshelbrenner, MD, Dr. Kristi Reynolds, PhD, Dr. Jiang He, MD, PhD, and Dr. Lydia A. Bazzano, MD, PhD

HİPERTANSİYONU OLMAYAN ama İNME DE DAHİL KARDİYOVASKÜLER HASTALIĞI OLAN HASTALARDA ANTİHİPERTANSİF TEDAVİ İLE KARDİYOVASKÜLER OLAYLARIN SEKONDER OLARAK ÖNLENMESİ
BİR META-ANALİZ ÇALIŞMASI

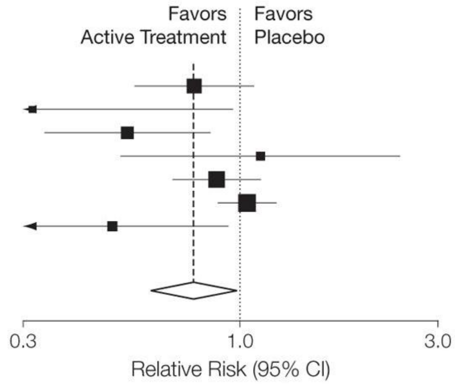
CVD events and all-cause mortality among persons without clinically defined hypertension.

Data Sources—Meta-analysis with systematic search of MEDLINE (1950 to week 3 of January 2011), EMBASE, and the Cochrane Collaboration Central Register of Controlled Clinical Trials and manual examination of references in selected articles and studies.

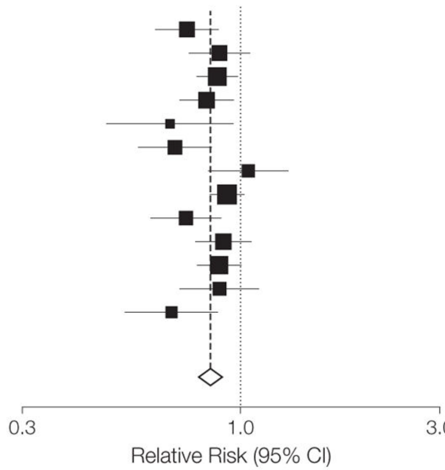
Study Selection—From 874 potentially relevant publications, 25 trials that fulfilled the predetermined inclusion and exclusion criteria were included in the meta-analysis.

Thompson A, et al. JAMA.2011;305:913-22.

Source	Events/Total, No. Placebo	Events/Total, No. Active	Relative Risk (95% CI)	Absolute Risk Reduction per 1000 (95% CI)
Fatal or nonfatal stroke				
SOLVD,[28] 1995	79/2077	62/2068	0.77 (0.56-1.08)	−8.1 (−19.1 to 3.0)
ABCD,[14] 2002	13/243	4/237	0.32 (0.10-0.95)	−36.6 (−69.3 to −3.9)
PEACE,[52] 2004	52/3071	27/2979	0.54 (0.34-0.85)	−7.9 (−13.6 to −2.2)
SAVE,[54] 2004	22/669	25/656	1.12 (0.51-2.44)	5.2 (−14.7 to 25.2)
PROGRESS,[56] 2006	121/1065	107/1072	0.88 (0.69-1.12)	−13.8 (−40.0 to 12.4)
PRoFESS,[61] 2008	259/3409	270/3413	1.04 (0.88-1.22)	3.1 (−9.6 to 15.8)
PATS,[65] 2009	28/470	13/443	0.49 (0.26-0.94)	−30.2 (−56.8 to −3.7)
Total	574/11 004	508/10 868		
Pooled relative risk			0.77 (0.61-0.98)	−7.7 (−15.2 to −0.3)
Heterogeneity: $P = .02$, $I^2 = 61.9\%$				



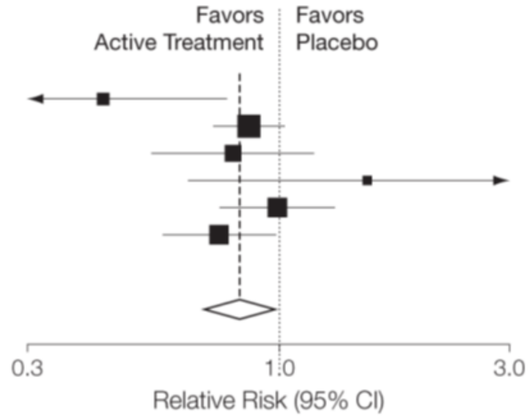
Source	Events/Total, No. Placebo	Events/Total, No. Active	Relative Risk (95% CI)	Absolute Risk Reduction per 1000 (95% CI)
Composite CVD outcomes				
SOLVD,[28] 1995	800/2077	629/2068	0.74 (0.62-0.89)	−81.0 (−109.8 to −52.2)
SMILE,[37] 1999	34/432	31/444	0.89 (0.75-1.05)	−8.9 (−43.6 to 25.9)
MERIT-HF,[40] 2000	414/1121	361/1114	0.88 (0.78-0.99)	−45.3 (−84.7 to −5.8)
HOPE,[43] 2002	370/2322	313/2351	0.83 (0.71-0.96)	−26.2 (−46.5 to −6.0)
CAMELOT,[12] 2004	77/359	51/340	0.68 (0.48-0.96)	−64.5 (−121.4 to −7.4)
COPERNICUS,[48] 2004[a]	NR	NR	0.70 (0.57-0.85)	NA
DIABHYCAR,[50] 2004	137/1112	137/1065	1.04 (0.84-1.30)	5.4 (−22.4 to 33.3)
PEACE,[52] 2004[a]	693/3071	624/2979	0.93 (0.84-1.02)	16.2 (−37.0 to 4.6)
SAVE,[54] 2004	234/669	180/656	0.74 (0.61-0.90)	−75.4 (−125.1 to −25.7)
ADVANCE,[59] 2007[b]	136/986	121/953	0.91 (0.78-1.06)	−11.0 (−41.1 to 19.2)
PRoFESS,[61] 2008	465/3409	414/3413	0.89 (0.79-1.01)	−15.1 (−31.0 to 0.8)
TRANSCEND,[15] 2008[a]	NR	NR	0.89 (0.72-1.11)	NA
EUROPA,[13] 2009[b]	387/4543	306/4611	0.78 (0.64-0.95)	−18.8 (−29.7 to −8.0)
Total	3747/20 101	3167/19 994		
Pooled relative risk			0.85 (0.80-0.90)	−27.1 (−40.3 to −13.9)
Heterogeneity: $P = .10$, $I^2 = 35.4\%$				

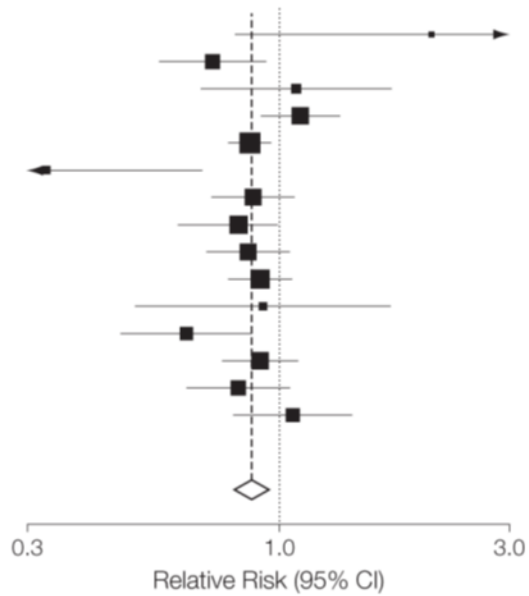


Tedavi alan hastalarda «inme» riskinde %23 azalma ve «tüm kardiyovasküler olay» riskinde %15 azalma saptanmış

Thompson A, et al. JAMA.2011;305:913-22.

Source	Events/Total, No. Placebo	Events/Total, No. Active	Relative Risk (95% CI)	Absolute Risk Reduction per 1000 (95% CI)
Cardiovascular mortality				
MIS,[22] 1975	36/678	15/656	0.43 (0.24-0.78)	–30.2 (–50.6 to –9.8)
TRACE,[33] 1997	204/675	176/674	0.86 (0.73-1.03)	–41.1 (–89.1 to 6.9)
AIRE,[36] 1999	48/717	38/715	0.80 (0.54-1.18)	–13.8 (–38.4 to 10.8)
ABCD,[14] 2002	9/243	13/237	1.48 (0.65-3.40)	17.8 (–19.7 to 55.3)
PEACE,[52] 2004	100/3071	96/2979	0.99 (0.75-1.30)	–0.3 (–9.3 to 8.6)
SAVE,[54] 2004	120/669	90/656	0.75 (0.57-0.98)	–42.2 (–81.4 to –3.0)
Total	517/6053	428/5917		
Pooled relative risk			0.83 (0.69-0.99)	–15.4 (–32.5 to 1.7)
Heterogeneity: $P=.12$, $I^2=43.6\%$				
All-cause mortality				
MPI,[23] 1980	6/143	13/149	2.07 (0.81-5.29)	45.3 (–10.7 to 101.3)
BHAT,[24] 1982	129/1369	92/1346	0.73 (0.56-0.94)	–25.9 (–46.4 to –5.4)
ASPS,[25] 1983	29/190	33/200	1.08 (0.68-1.71)	12.4 (–60.2 to 84.9)
CONSENSUS II,[26] 1992	190/2259	202/2178	1.10 (0.91-1.33)	8.6 (–8.1 to –25.4)
SOLVD,[28] 1995	501/2077	426/2068	0.87 (0.78-0.96)	–35.2 (–60.6 to –9.9)
USCHF,[32] 1996	19/210	13/337	0.34 (0.17-0.69)	–51.9 (–95.8 to –8.0)
TRACE,[33] 1997	267/675	233/674	0.88 (0.72-1.07)	–49.9 (–101.3 to 1.6)
AIRE,[36] 1999	148/717	116/715	0.78 (0.61-0.99)	–44.2 (–84.3 to –4.1)
SMILE,[37] 1999	25/432	22/444	0.86 (0.70-1.05)	–8.3 (–38.2 to 21.6)
CCS-1,[41] 2001	303/2354	282/2406	0.91 (0.78-1.06)	–11.5 (–30.2 to 7.2)
ABCD,[14] 2002	20/243	18/237	0.92 (0.50-1.70)	–6.4 (–54.6 to 41.9)
COPERNICUS,[48] 2004	NR	NR	0.64 (0.47-0.88)	NA
PEACE,[52] 2004	230/3071	203/2979	0.91 (0.76-1.09)	–6.8 (–19.7 to 6.2)
SAVE,[54] 2004	140/669	115/656	0.82 (0.64-1.05)	–34.0 (–76.4 to 8.4)
PROGRESS,[56] 2006	84/1065	90/1072	1.06 (0.80-1.41)	5.1 (–18.1 to 28.3)
Total	2091/15 474	1858/15 461		
Pooled relative risk			0.87 (0.80-0.95)	–13.7 (–24.6 to –2.8)
Heterogeneity: $P=.03$, $I^2=46.1\%$				





Tedavi alan hastalarda «kardiyovasküler mortalite» riskinde %17 ve «tüm nedenlere bağlı mortalite» riskinde %13 azalma saptanmış

Thompson A, et al. JAMA.2011;305:913-22.

PRoFESS trial post hoc analysis

JAMA. 2011 Nov 16;306(19):2137-44.

Level of systolic blood pressure within the normal range and risk of recurrent stroke.

Ovbiagele B , Diener HC, Yusuf S, Martin RH, Cotton D, Vinisko R, Donnan GA, Bath PM; PROFESS Investigators.

Normal Aralıktaki SKB Düzeyi ile Tekrarlayan İnme Riski Arasındaki İlişki

Abstract

CONTEXT: Recurrent stroke prevention guidelines suggest that larger reductions in systolic blood pressure (SBP) are positively associated with a greater reduction in the risk of recurrent stroke and define an SBP level of less than 120 mm Hg as normal. However, the association of SBP maintained at such levels with risk of vascular events after a recent ischemic stroke is unclear.

OBJECTIVE: To assess the association of maintaining low-normal vs high-normal SBP levels with risk of recurrent stroke.

DESIGN, SETTING, AND PATIENTS: Post hoc observational analysis of a multicenter trial involving 20,330 patients (age ≥50 years) with recent non-cardioembolic ischemic stroke; patients were recruited from 695 centers in 35 countries from September 2003 through July 2006 and followed up for 2.5 years (follow-up ended on February 8, 2008). Patients were categorized based on their mean SBP level: very low-normal (<120 mm Hg), low-normal (120-<130 mm Hg), high-normal (130-<140 mm Hg), high (140-<150 mm Hg), and very high (≥150 mm Hg).

MAIN OUTCOME MEASURES: The primary outcome was first recurrence of stroke of any type and the secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes.

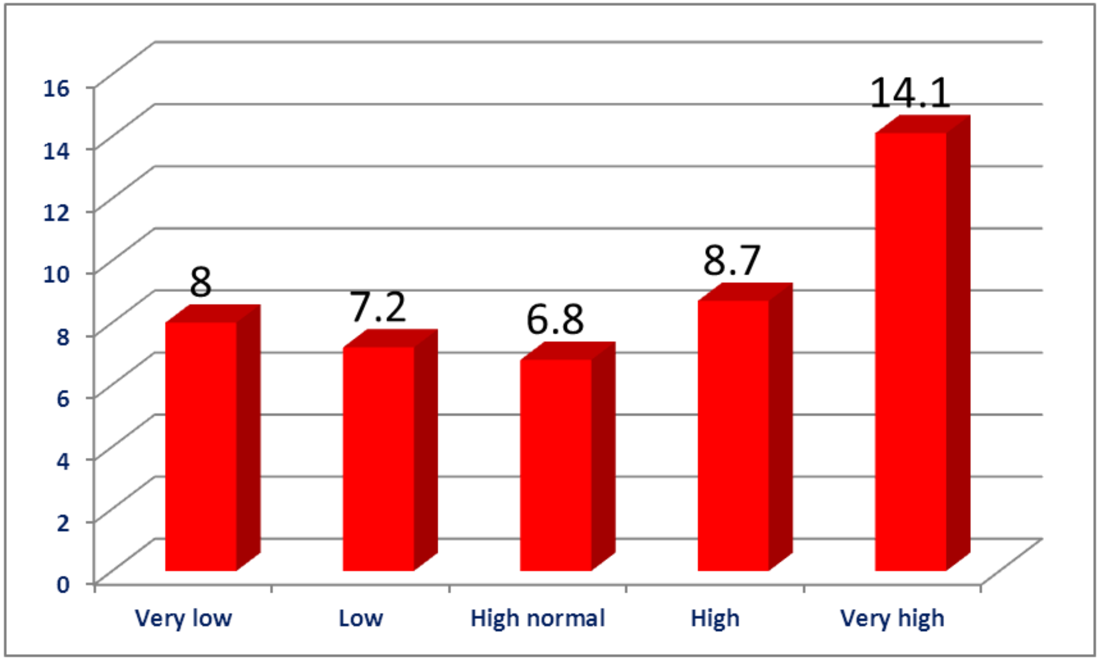


Table 4. Adjusted Risk of Clinical Outcomes by Mean Systolic Blood Pressure Level in 20 330 Patients With a Recent Ischemic Stroke

	Mean Systolic Blood Pressure Level, mm Hg				
	High-Normal (130-<140; n = 6004)	Very Low–Normal (<120; n = 1919)	Low-Normal (120-<130; n = 3982)	High (140-<150; n = 4520)	Very High (≥150; n = 3905)
AHR (95% CI)					
Stroke[a]	1 [Reference]	1.29 (1.07-1.56)	1.10 (0.95-1.28)	1.23 (1.07-1.41)	2.08 (1.83-2.37)
Stroke, MI, or vascular death[b]	1 [Reference]	1.31 (1.13-1.52)	1.16 (1.03-1.31)	1.24 (1.11-1.39)	1.94 (1.74-2.16)
Fatal stroke[c]	1 [Reference]	0.63 (0.26-1.49)	1.01 (0.64-1.89)	1.50 (0.94-2.40)	2.51 (1.62-3.09)

Non-kardiyoembolik iskemik inmeli hastalarda, çok düşük (<120 mmHg), yüksek (140- <150 mmHg) ve çok yüksek (≥150 mmHg) SKB düzeyleri artmış «tekrarlayan inme» riski ve «bileşik sonlanım noktası-inme, MI veya vasküler nedenli ölüm-» ile ilişkilidir.

J EĞRİSİ FENOMENİ VE TEKRARLAYAN İNME RİSKİ

The J-Curve Phenomenon in Stroke Recurrence

Katsumi Irie, MD; Takenori Yamaguchi, MD; Kazuo Minematsu, MD; Teruo Omae, MD

Background and Purpose: The relation of poststroke blood pressure to stroke recurrence remains undetermined, and the optimal control of blood pressure has not been established. We performed the present study to resolve these issues.

Methods: We analyzed 368 stroke patients with a history of hypertension (mean age, 62 years) who were admitted within 3 months after stroke onset and observed for 6 months or more. We determined stroke recurrence rate in relation to baseline (or initial) blood pressure, mean values of poststroke blood pressure, stroke subtypes, age, antihypertensive treatment, and other clinical features.

Results: The recurrence rate had a J-curve relation to poststroke diastolic blood pressure but not to poststroke systolic blood pressure and baseline diastolic and systolic blood pressures. The stroke recurrence rate was 3.8% per patient-year in 94 patients who had a poststroke diastolic blood pressure of 80 to 84 mm Hg, significantly lower than the rates of 9.2% per patient-year ($P<.05$) and 11.4% per patient-year ($P<.01$) in those with a lower and higher poststroke diastolic blood pressure, respectively. The range of poststroke diastolic blood pressure accompanying the lowest stroke recurrence rate was higher in patients with atherothrombotic (85 to 89 mm Hg) than in those with lacunar infarction (80 to 84 mm Hg). Neither antihypertensive therapy nor patients' age affected this phenomenon.

Conclusions: The present study suggests that lower blood pressure does not always result in favorable effects on stroke recurrence. The effects of poststroke blood pressure and antihypertensive therapy on stroke recurrence may be complicated by the J-curve phenomenon. (*Stroke*. 1993;24:1844-1849.)

- İnmeden sonraki 3 ay dönem içindeki inmeli hastalar çalışmaya alınıyor ve en az 6 ay takip ediliyor
- HT; SKB >160 mmHg, DKB >95 mmHg olması veya hastanın antipertansif tedavi alması şeklinde tanımlanıyor
- 254 hasta antihipertansif tedavi alırken, 114 hasta tedavi almıyor

Table 1. Effect of Baseline and Poststroke Blood Pressure on Stroke Recurrence

	Baseline BP		Poststroke BP	
	n	Recurrence Rate, %/patient-year	n	Recurrence Rate, %/patient-year
SBP, mm Hg				
<140	56	5.11	109	5.30
140-149	58	5.07	100	3.98
150-159	78	4.32	81	12.19†
160-169	58	12.32*	54	11.00†
≥170	58	8.13	24	14.75†
DBP, mm Hg				
<80	62	6.93	98	9.20‡
80-84	54	5.77	94	3.75
85-89	57	6.70	85	6.72
90-94	47	6.32	45	11.56§
≥95	88	7.26	46	11.31‡

BP indicates blood pressure; S, systolic; and D, diastolic.
*P<.01 vs baseline SBP 150-159 mm Hg.
†P<.01 vs poststroke SBP 140-149 mm Hg.
‡P<.05, §P<.01 vs poststroke DBP 80-84 mm Hg, by log-rank test.

J eğrisi fenomeni

- J eğrisi fenomeni iskemik inmeli hastalarda gözlenirken, hemorajik inmeli hastalarda gözlenmemiş
- J noktası aterotrombotik infarktlı hastalarda, laküner infartlı hastalardan daha yüksekte
- Yaş ve antihipertansif tedavi bu fenomeni etkilemiyor

Irie K et al. Stroke 1993;24:1844-9.

- Hedef KB düzeyi veya tedavi öncesi bazal düzeyden ne kadar düşürüleceği belirsizdir ama hedefler her hasta için bireyselleştirilmelidir**

ama

- SKB <140 mmHg ve DKB <90 mmHg hedefi mantıklı (Class IIa; kanıt düzeyi B)**
- Laküner inmeli hastalar için SKB <130 mmHg hedefi mantıklı olabilir (Class IIb; kanıt düzeyi B)**

**AHA/ASA guideline,Kernan WN, et al. Stroke. 2014 ;45:2160-236

Relationship Between Blood Pressure and Stroke Risk in Patients With Symptomatic Carotid Occlusive Disease

P.M. Rothwell, PhD; S.C. Howard, DPhil; J.D. Spence, MD;
for the Carotid Endarterectomy Trialists' Collaboration

Background and Purpose—Blood pressure lowering in patients with a previous transient ischemic attack (TIA) or stroke reduces the risk of recurrent stroke and coronary vascular events. However, there is uncertainty about the risks and benefits in patients with severe carotid occlusive disease, particularly those with a carotid occlusion or bilateral ≥70% carotid stenosis in whom cerebral perfusion is often impaired and may depend directly on systemic blood pressure. Therefore, we studied the effect of carotid artery disease on the relationship between blood pressure and stroke risk in patients with recent TIA or stroke.

Methods—We compared the relationship between blood pressure (systolic and diastolic blood pressures, pulse pressure) and stroke risk in TIA and stroke patients with documented stenosis of at least 1 carotid artery [European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET)] with that in TIA and stroke patients with a low prevalence of carotid disease [United Kingdom Transient Ischaemic Attack (UK-TIA) Aspirin Trial]. In ECST and NASCET, we also determined the relationship between blood pressure and stroke risk in patients with unilateral carotid occlusion and patients with bilateral ≥70% carotid stenosis.

Results—Stroke risk on medical treatment increased with blood pressure in ECST and NASCET, but the relationships were less steep than in the UK-TIA trial. The relationship between blood pressure and stroke risk was not affected by the presence of a unilateral carotid occlusion but was significantly affected by the presence of bilateral carotid stenosis ≥70% (interaction: systolic blood pressure, $P=0.002$; diastolic blood pressure, $P=0.03$; pulse pressure, $P=0.003$). In this group, the relationship was inverted because of the high stroke risks at lower blood pressures. This interaction was not present after carotid endarterectomy and was not present for the risk of myocardial infarction.

Conclusions—The risk of stroke increases with blood pressure in the great majority of patients with symptomatic carotid artery disease, but the relationship is less steep than in other patients with TIA or stroke. The relationship is unaffected by unilateral carotid occlusion alone but is inverted in patients with bilateral ≥70% carotid stenosis, suggesting that aggressive blood pressure lowering may not be advisable in this group. These patients represent only a few percent of all patients with TIA or stroke but have a high risk of recurrent stroke. (*Stroke*. 2003;34:2583-2592.)

Key Words: blood pressure ■ carotid endarterectomy ■ carotid stenosis ■ hypertension

Bilateral semptomatik (≥%70) karotid arter stenozu olan hastalarda kan basıncının agresif düşürülmesi tekrarlayan inme riskini artırır

- **Büyük servikosefalik arterlerde (internal karotid, vertabral, baziller veya orta serebral arter) hemodinamik veya klinik olarak anlamlı darlığı olan hastalar**
- Spesifik bir kan basıncı hedefi olmaksızın, hastanın tolere edebildiği bir kan basıncına dikkatli bir şekilde düşürmek uygundur*
- Eğer kan basıncı belirli bir eşik düzeyin altına düştüğünde nörolojik bulgular gelişiyorsa, kan basıncının bu eşik değerin üstünde tutulması öneriliyor*

*Kaplan NM, Uptodate 2015

- **Büyük servikosefalik arterlerde hemodinamik veya klinik olarak anlamlı (internal karotid, vertabral, baziller veya orta serebral arter) darlığı olan hastalar**
- Bazal kan basıncı 120/70 mmHg'den düşük ise antihipertansif tedavi önerilmiyor*
- Hemodinamik olarak belirgin stenotik arter endarterektomi veya stent ile düzeltilirse, kan basıncı hedeflerinin kademeli olarak stenozu olmayan hastalarda olan düzeye çekilmesi öneriliyor*

*Kaplan NM, Uptodate 2015

İNMELİ HASTALARDA KAN BASINCI KONTROLÜ NE DURUMDA?

Secondary Prevention of Stroke in Italy
A Cross-Sectional Survey in Family Practice

(*Stroke*. 2003;34:1010-1014.)

Alessandro Filippi, MD; Angelo Antonio Bignamini, PhD; Emiliano Sessa; Fabio Samani, MD; Giampiero Mazzaglia, MD, PhD, MSc

Results—We selected 2555 patients with diagnosis of stroke and 2755 with TIA. Among all of the subjects, 32.6% had no BP recorded. Among the remaining subjects, 58.7% reported uncontrolled BP. Isolated systolic hypertension has

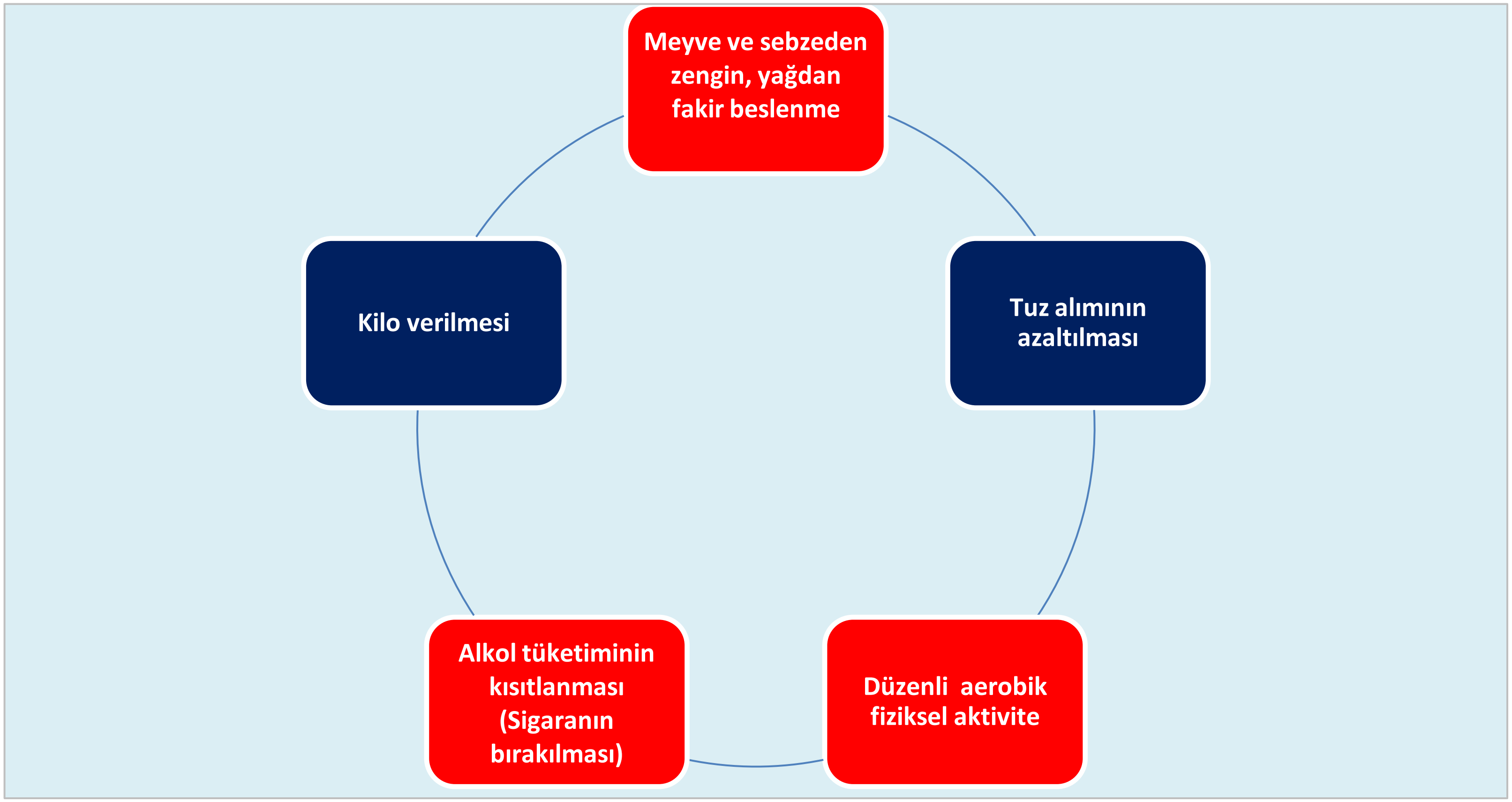
JAMA. 2011 Nov 16;306(19):2137-44. doi: 10.1001/jama.2011.1650.

Level of systolic blood pressure within the normal range and risk of recurrent stroke.

Ovbiagele B[1], Diener HC, Yusuf S, Martin RH, Cotton D, Vinisko R, Donnan GA, Bath PM; PROFESS Investigators.

İnmeli hastalar kan basıncı kontrolü yetersiz;
Yaklaşık %40-60'ında SKB 140 mmHg'nin üstünde

YAŞAM TARZI DEĞİŞİKLERİ



Class IIa; kanıt düzeyi C**

**AHA/ASA guideline,Kernan WN, et al. Stroke. 2014 ;45:2160-236

ÖZET

- Hipertansiyon inme için önemli bir risk faktörüdür
- Genel olarak, kan basıncını düşürücü tedavi tekrarlayan inme riskinde anlamlı bir azalma ile ilişkilidir
- İnme stabilize olduktan sonra kronik faz için antihipertansif tedaviye geçilmelidir
- Spesifik hasta özellikleri göz önünde bulundurularak tedavi kişiselleştirilmelidir
- Tiyazidler, RAS blokerleri, kalsiyum kanal blokerleri inmeli hastalarda başlangıç monoterapi için uygun seçenekler olabilir ama beta blokerler ilk tercih olmamalı
- Kombinasyon tedavisi için;

  ACE inhibitörü + bir diüretik

  RAS blokeri + CCB

ÖZET

- Hedef KB düzeyi her hasta için bireyselleştirilmelidir
- SKB <140 mmHg ve DKB <90 mmHg hedefi mantıklı
- Laküner inmeli hastalar için SKB <130 mmHg hedefi mantıklı olabilir
- Büyük servikosefalik arterlerde anlamlı darlığı olan hastalarda spesifik bir kan basıncı hedefi olmaksızın, hastanın tolere edebildiği bir kan basıncına dikkatli bir şekilde düşürmek uygundur

SON OLARAK

- Kan basıncının düşüşüne yanıtta bireysel farklılıklar olabilir
- Hedef değere kan basıncını titre ederken, bu ayarlamayı nörolojik durumu yakından izleyerek, tedrici ve ihtiyatlı yaparsak çoğu hasta kan basıncı düşüşünü tolere edecektir

TEŞEKKÜRLER

“10 yıl içinde, size öğretilenlerin %50’sinin yanlış olduğu gösterilecek...
Tek problem hangi %50?”

Charles Sidney Burwell
Harvard Tıp Fakültesi Dekanı 1949

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2008 VOL. 359 NO. 23

Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

BACKGROUND

The optimal combination drug therapy for hypertension is not established, although current U.S. guidelines recommend inclusion of a diuretic. We hypothesized that treatment with the combination of an angiotensin-converting–enzyme (ACE) inhibitor and a dihydropyridine calcium-channel blocker would be more effective in reducing the rate of cardiovascular events than treatment with an ACE inhibitor plus a thiazide diuretic.

METHODS

In a randomized, double-blind trial, we assigned 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization.

End Point	Benazepril–Amlodipine Group (N=5744)	Benazepril–Hydrochlorothiazide Group (N=5762)	Hazard Ratio (95% CI)*	P Value†
Primary				
Composite of cardiovascular events and death from cardiovascular causes — no. (%)	552 (9.6)	679 (11.8)	0.80 (0.72–0.90)	<0.001
Individual component — no (%)				
Death from cardiovascular causes	107 (1.9)	134 (2.3)	0.80 (0.62–1.03)	0.08

Yüksek riskli hipertansif hastalarda kardiyovasküler olayları azaltmada benazepril-amlodipin kombinasyonu benazepril-hidroklortiyazid kombinasyonundan daha iyidir.

Composite of death from cardiovascular events, non-fatal myocardial infarction, and nonfatal stroke — no. (%)	288 (5.0)	364 (6.3)	0.79 (0.67–0.92)	0.002
Death from any cause — no. (%)	236 (4.1)	262 (4.5)	0.90 (0.76–1.07)	0.24
Hospitalization for congestive heart failure — no. (%)	100 (1.7)	96 (1.7)	1.04 (0.79–1.38)	0.77
Primary end point plus hospitalization for congestive heart failure — no. (%)	617 (10.7)	738 (12.8)	0.83 (0.74–0.92)	0.0005

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

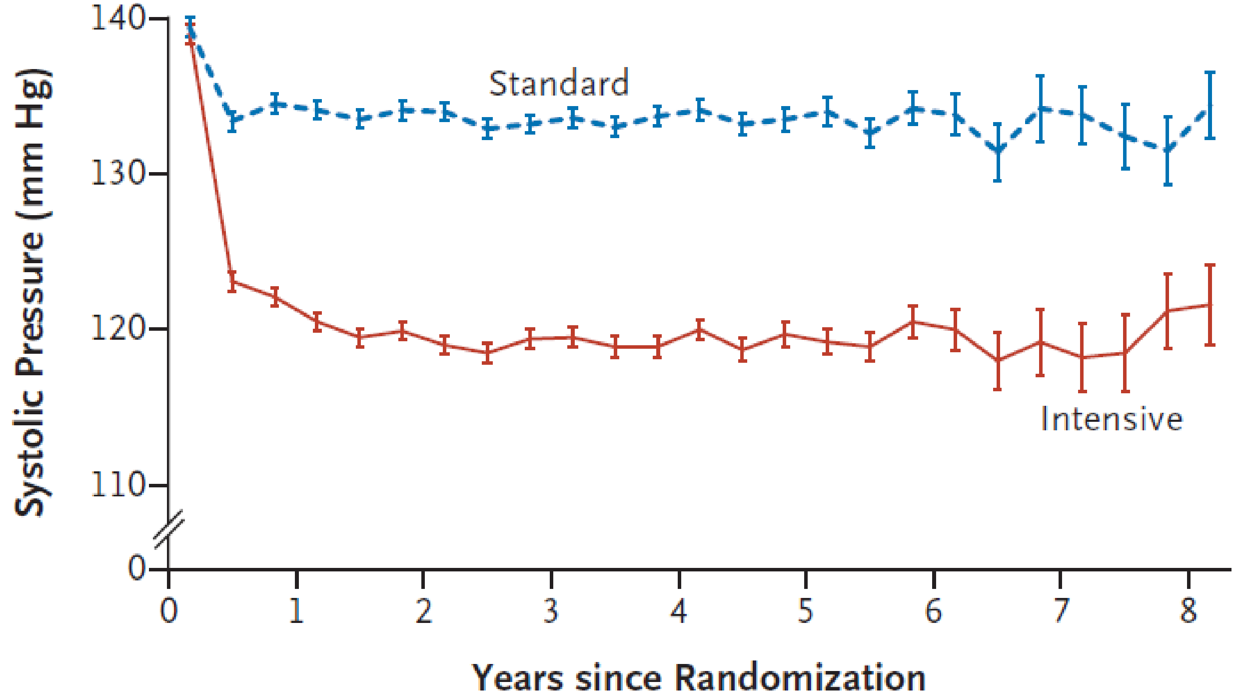
The ACCORD Study Group*

Kardiyovasküler olaylar için yüksek riskli tip 2 diyabetik hastalarda normal sistolik kan basıncını (<120 mmHg) hedefleyen tedavinin majör kardiyovasküler olayları azaltıp azaltmadığını araştırmak

*4733 hasta yoğun tedavi (hedef SKB<120 mmHg) ve standart tedavi (hedef SKB<140 mmHg) kollarına ayrılıyor.
*Primer sonlanım noktası: nonfatal MI, nonfatal inme, kardiyasküler nedenlere bağlı ölüm
*Takip süresi ortalama 4.7 yıl

ACCORD study group. NEJM. 2010;362:1575-1585

1. yıl sonunda yoğun tedavi kolunda SKB 119.3 mmHg, standart tedavi kolunda 133.5 mmHg



	1	2	3	4	5	6	7	8
Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

ACCORD study group. NEJM. 2010;362:1575-1585

Table 3. Primary and Secondary Outcomes.

Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.

ACCORD study group. NEJM. 2010;362:1575-1585

Variable	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Serious adverse events — no. (%)†			
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	12 (0.5)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12
End-stage renal disease or need for dialysis	59 (2.5)	58 (2.4)	0.93

CONCLUSIONS

In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)

ACCORD study group. NEJM. 2010;362:1575-1585

PROGRESS: Prevention of Recurrent Stroke

Hisatomi Arima, MD, PhD; John Chalmers, MD, PhD

From The George Institute for Global Health, University of Sydney and the Royal Prince Alfred Hospital, Sydney, Australia

PROGRESS çalışma grubu meta-analizi

	Year	1st Listed Event	1st Listed N	2nd Listed Event	2nd Listed N	Relative Risk (95% CI)
Active vs control						
Carter	1970	10	50	21	49	0.47 (0.25-0.89)
HSCSG	1974	37	233	42	219	0.83 (0.55-1.24)
Dutch TIA	1993	52	732	62	741	0.85 (0.60-1.21)
TEST	1995	81	372	75	348	1.01 (0.77-1.33)
PATS	1995	159	2841	217	2824	0.73 (0.60-0.89)
INDANA	1997					
EWPHE		5	35	9	28	0.44 (0.17-1.18)
Coope		2	11	1	6	1.09 (0.12-9.70)
HDFP		15	136	16	138	0.95 (0.49-1.85)
SHEP		8	59	7	40	0.78 (0.31-1.97)
STOP		1	31	4	35	0.28 (0.03-2.39)
HOPE	2000	43	500	51	513	0.87 (0.59-1.27)
PROGRESS	2001	307	3051	420	3054	0.73 (0.64-0.84)
SCOPE	2003	6	97	15	97	0.40 (0.16-0.99)
FEVER	2005	66	1136	87	1232	0.82 (0.60-1.12)
PRoFESS	2008	880	10146	934	10186	0.95 (0.87-1.03)
Subtotal						**0.81 (0.73-0.91)**
Test for homogeneity: chi-square=23.03, df=14 (*P*=.06)						
Test for overall effect: Z=3.70 (*P*<.001)						
ARB vs CCB						
MOSES	2005	80	681	89	671	0.89 (0.67-1.18)
Total						**0.82 (0.74-0.91)**
Test for homogeneity: chi-square=23.09, df=15 (*P*=.08)						
Test for overall effect: Z=3.87 (*P*<.001)						

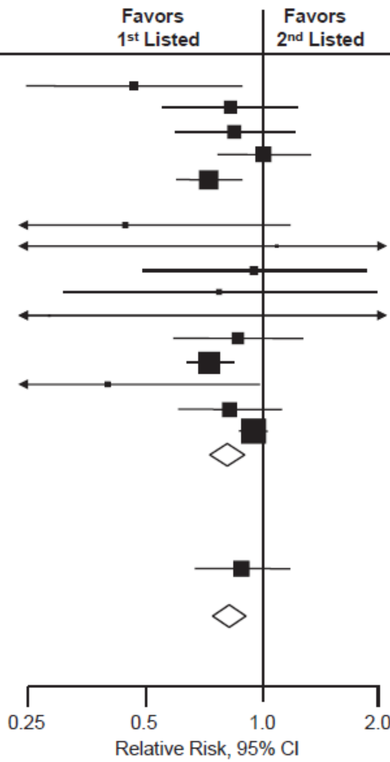


FIGURE 8. Meta-analysis of 16 randomized controlled trials of blood pressure lowering for secondary prevention of stroke.[9,11,12,40–43,46] Solid boxes represent estimates of trials. Diamonds represent estimates and 95% confidence intervals (CIs) for overall effects. Overall estimates of effect and 95% CI were calculated using random-effects models and inverse variance weighting. See text for trial name expansions.

KB düşürücü tedavi «tekrarlayan inme» riskini %18 azaltır
SKB'de her 10 mmHg düşüş riski %33 azaltır

Arima H and Chalmers J. J Clin Hypertens. 2011;13:693-702.

- İnmeden hemen sonra kan basıncı yönetimi tartışmalıdır
- Kronik hipertansif hastalarda otoregülasyon hasarlı olabileceği için, kan basıncının düşürülmesi, en azından teorik olarak, serebral perfüzyonu azaltabilir ve olayı kötüleştirebilir

Is lowering blood pressure hazardous in patients with significant ipsilateral carotid stenosis and acute ischaemic stroke? Interim assessment in the 'Efficacy of Nitric Oxide in Stroke' Trial

Gillian M. Sare[a], Laura J. Gray[a], Joanna Wardlaw[b], Christopher Chen[c], Philip M.W. Bath[a] and for the ENOS Trial Investigators

METHODS: Efficacy of Nitric Oxide in Stroke (ENOS) is an international, randomized controlled trial investigating the effect of lowering BP with glyceryl trinitrate in 5000 patients with acute stroke. This analysis is based on patients with ischaemic stroke for whom information on the carotid status was available. Neurological impairment (Scandinavian Stroke Scale) and rate of recurrent stroke were assessed on day 7, and the functional outcome (modified Rankin score) was determined on day 90. ENOS is ongoing, therefore analyses are blinded to treatment.

RESULTS: At the time of analysis, 565 patients with ischaemic stroke had been randomized into ENOS and data on carotid status were available in 394 (70%) of these patients. Ipsilateral

Blood Press Monit. 2009;14:20-5.

Table 1 Baseline characteristics of all trial patients with Ischaemic stroke and by carotid duplex results of the symptomatic hemisphere where available

	All IS, n=565 (SD/%)	Stenosis <50%, n=344 (SD/%)	Stenosis ≥ 50%, n=50 (SD/%)	Stenosis ≥ 70%, n=36 (SD/%)	P value (<50 vs. ≥ 50%)
Age (years)	69.5 (11.3)	67.6 (11.0)	68.5 (13.0)	67.4 (12.4)	0.58
Sex (male)	312 (55)	201 (58)	26 (52)	22 (61)	0.45
Baseline SSS	35.8 (13.5)	38.0 (12.5)	33.5 (13.0)	31.9 (13.3)	0.02
Baseline SBP (mmHg)	167.5 (20.1)	167.3 (19.5)	164.6 (16.8)	164.6 (16.4)	0.35
Baseline DBP (mmHg)	89.7 (13.4)	91.6 (13.3)	84.3 (10.7)	83.2 (8.8)	<0.0001
History of hypertension	383 (68)	232 (68)	38 (76)	26 (72)	0.26
Prestroke antihypertensive	270 (48)	163 (47)	30 (60)	17 (47)	0.10
History of DM	133 (24)	92 (27)	8 (16)	5 (14)	0.12
History of AF	65 (12)	26 (8)	5 (10)	1 (3)	0.57
History of previous stroke	77 (14)	50 (15)	5 (10)	4 (11)	0.52
Time to randomization (h)	30.7 (14.9)	31.5 (11.5)	27.0 (12.3)	27.1 (12.4)	0.01

AF, atrial fibrillation; DBP, diastolic blood pressure; DM, diabetes mellitus; IS, ischaemic stroke; SBP, systolic blood pressure; SD, standard deviation; SSS, Scandinavian Stroke Scale.

Table 2 Summary of events at day 7 for all ischaemic stroke trial patients and by carotid duplex results of the symptomatic hemisphere where available

Event	All IS n=565 (%)	Stenosis <50% n=344 (95% CI)	Stenosis ≥ 50% n=50 (95% CI)	P value (<50 vs. ≥ 50% stenosis)
Death	12 (2.1)	3 (0.9, 0.2–2.7)	0 (0, 0–9.0)	0.66
Recurrent stroke	10 (1.8)	6 (1.7, 0.7–3.8)	0 (0, 0–9.0)	0.44
Neurological deterioration	44 (7.8)	24 (7.0, 4.3–10.3)	4 (8.0, 2.6–20.1)	0.49
SSS	40.9 (14.7)[a]	43.2 (13.3)[a]	38.3 (13.4)[a]	0.48[b]

Frequency (%) of events with 95% confidence intervals (CI) is shown. Comparison by Fisher's exact test.
Neurological deterioration, fall in SSS ≥ 5 from baseline; IS, ischaemic stroke; SSS, Scandinavian Stroke Scale.

CONCLUSION: Interim data provide reassurance that it is reasonable to continue including patients with carotid stenosis into trials of acute BP lowering (such as ENOS).

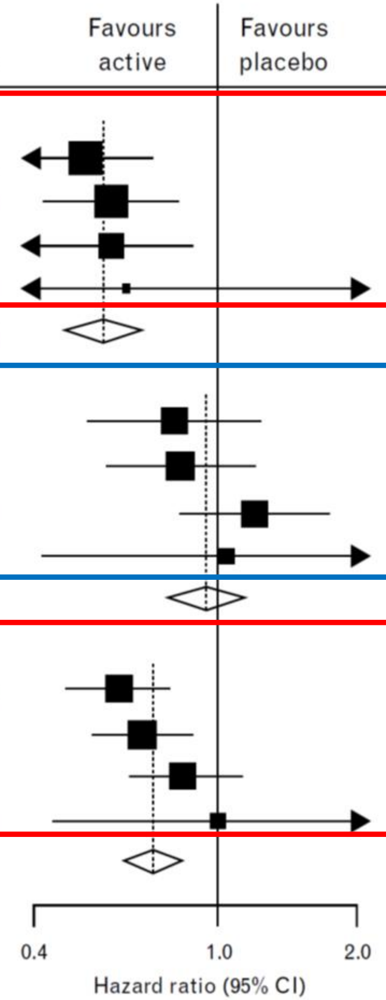
Selected Adverse Events Leading to Discontinuation of a Study Drug

Adverse Event	Telmisartan (N = 10,146)	Placebo (N = 10,186)	P Value
	no. (%)		
Total	1450 (14.3)	1127 (11.1)	<0.001
Hypotensive symptoms	393 (3.9)	186 (1.8)	<0.001
Syncope	21 (0.2)	6 (0.1)	0.004
Uncontrolled hypertension	13 (0.1)	17 (0.2)	0.47
Headache	231 (2.3)	203 (2.0)	0.16
Diarrhea	69 (0.7)	45 (0.4)	0.02
Nausea	104 (1.0)	72 (0.7)	0.01
Vomiting	74 (0.7)	61 (0.6)	0.25
Angioedema	23 (0.2)	31 (0.3)	0.28
Renal impairment	28 (0.3)	18 (0.2)	0.14
Hyperkalemia	14 (0.1)	6 (0.1)	0.07
Atrial fibrillation	81 (0.8)	50 (0.5)	0.006

Yusuf S, et al. N Engl J Med. 2008;359:1225-37

PROGRESS çalışması-post hoc analizi
Bazal KB değerlerine göre bir analiz

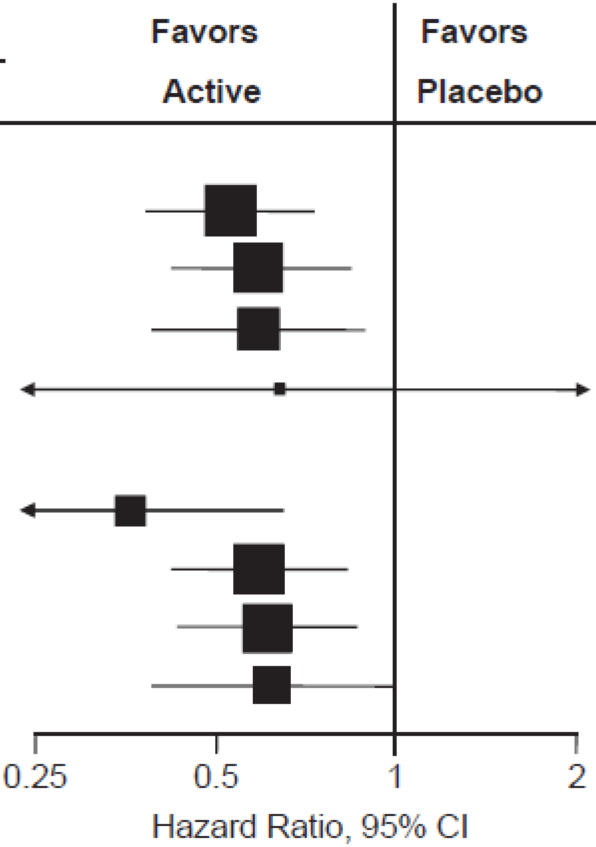
SBP (mmHg)	Events/patients Active	Events/patients Placebo	Combination therapy	SBP difference	Risk reduction (95% CI)	*P* trend
Combination therapy						
≥160	57/524	106/543		14.2 mmHg	47 (27 to 62)	0.5
140 to 159	54/695	87/689		12.2 mmHg	41 (16 to 58)	
120 to 139	37/486	58/461		9.7 mmHg	41 (11 to 61)	
<120	2/65	4/81		9.3 mmHg	36 (−249 to 88)	
Total	150/1770	255/1774		12.3 mmHg	43 (30 to 54)	
Single-drug therapy						
≥160	38/263	43/242		4.4 mmHg	19 (−25 to 48)	0.2
140 to 159	51/497	63/515		4.8 mmHg	16 (−21 to 42)	
120 to 139	58/412	51/428		5.2 mmHg	−21 (−76 to 17)	
<120	10/109	8/95		5.7 mmHg	−6 (−169 to 58)	
Total	157/1281	165/1280		4.9 mmHg	5 (−19 to 23)	
All participants						
≥160	95/787	149/785	68%	11.1 mmHg	39 (−21 to 53)	0.05
140 to 159	105/1192	150/1204	58%	9.2 mmHg	31 (−11 to 46)	
120 to 139	95/898	109/889	53%	7.6 mmHg	14 (−13 to 35)	
<120	12/174	12/176	42%	7.4 mmHg	0 (−123 to 55)	
Total	307/3051	420/3054	58%	9.0 mmHg	28 (−17 to 38)	



Arima H, et al. J Hypertens 2006;24:1201-8.

PROGRESS çalışması-post hoc analizi Kombinasyon kolunda bazal KB değerlerine göre bir analiz

	Number of Events: Active	Number of Events: Placebo	Risk Reduction (95% CI)	*P* Homogeneity
Systolic blood pressure				
≥160 mm Hg	57	106	47% (27 to 62%)	0.5
140 to 159 mm Hg	54	87	41% (16 to 58%)	
120 to 139 mm Hg	37	58	41% (11 to 61%)	
<120 mm Hg	2	4	36% (-249 to 88%)	
Diastolic blood pressure				
≥100 mm Hg	16	40	64 %(35 to 80%)	0.2
90 to 99 mm Hg	53	84	41% (17 to 58%)	
89 to 90 mm Hg	52	85	39% (14 to 57%)	
<80 mm Hg	49	46	38% (1 to 61%)	



- **Hemodinamik olarak anlamlı büyük arter stenozu olmayan hastalar**
- Minimum 10/5 mmHg’lık bir kan basıncı düşüşü öneriliyor*
- Bazal kan basıncı 120/70 mmHg’den düşük ise antihipertansif tedavi önerilmiyor*
- Altta yatan hipertansiyonu olan hastalarda 140/90 mmHg’den daha düşük bir kan basıncı hedeflenmeli ve eğer tedavi belirgin yan etkilere neden olmuyorsa sistolik kan basıncını 130-135 mmHg’nin altına düşürmek öneriliyor (zayıf bir öneri)*
- Laküner (küçük damar hastalığı) iskemik inmeli hastalarda sistolik kan basıncını 130 mmHg’nin altına düşürmek öneriliyor (zayıf bir öneri)*

*Kaplan NM, Uptodate 2015