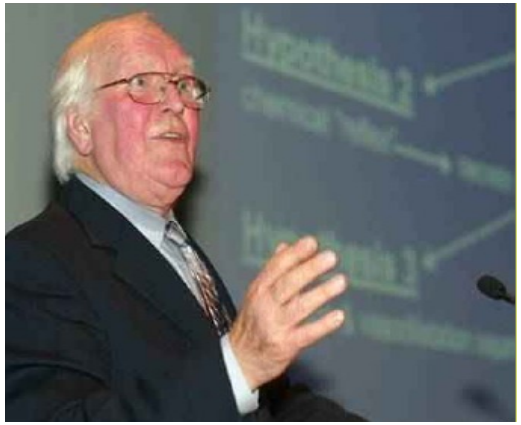
β-BLOKÖRLER NEREYE KOŞUYOR

Doç. Dr. İbrahim İKİZCELİ

İ.Ü. Cerrahpaşa Tıp Fakültesi
Acil Tıp Anabilim Dalı

Adernerjik sistem Tarihçesi



James Black
Nobel Tıp Ödülü
"Propranolol keşfi"

1900-1910
- Epinefrin

1940-1950
- Norepinefrin
- α, β-reseptör

1950-1960
- c-AMP

1960-1970
- Propranolol
- β1- β2 subtipleri

1970-1980
- α1 -α2

1980-1990
- α1A , α1B, α2C
- β3

1990-2000
- α1D
- β4?

Table 1. Sites of action and physiological effects for the respective β-adrenergic receptors

Receptor	Site of action	Physiological effect
β_1	Heart	↑ Chronotropy, ↑ inotropy, ↑ AV node conduction velocity
	Juxtaglomerular cells	↑ Renin production
β_2	Smooth muscle	↑ Relaxation in vessels, bronchi, gastrointestinal tract, and genitourinary tract
	Skeletal muscle	↑ Glycogenolysis and potassium uptake
	Liver	↑ Glycogenolysis and gluconeogenesis
	Pancreas	↑ Insulin and glucagon secretion
	Thyroid	↑ Conversion of T4 to T3
β_3	Adipose tissue	↑ Lipolysis and thermogenesis

AV, atrioventricular.

Adapted from Mason et al.[3]

Table 2. Pharmacological properties of the different β-blockers

Drug	β_1-Blockade potency ratio	β1/β2 selectivity	ISA	Lipophilicity	MSA	Half-life (h)	Other
Non-selective β-blockers							
Nadolol	1.0	0	0	Low	0	12-24	
Pindolol	6.0	0	++	High	+	3-4	
Propranolol	1.0	0	0	High	++	3-4	
Sotalol	0.3	0	0	Low	0	12	Antiarrythmic effects
Timolol	0.6	0	0	High	0	4-5	
Selective β-blockers							
Acebutolol	0.3	+	+	Moderate	+	3-4	
Atenolol	1.0	+	0	Low	0	6-9	
Bisoprolol	10.0	++	0	Moderate	0	9-12	
Esmolol (IV)	NA	++	0	Low	0	9 min	
Metoprolol	1.0	++	0	High	0	3-4	
α- and β-blockers							
Labetolol	0.3	+	0	Low	0	3-4	α_1-Blocking effect, direct β-vasodilation
Carvedilol	10.0	0	0	Moderate	++	7-10	α_1-Blocking effect
Selective β-blocker with ancillary properties							
Nebivolol	10.0	+++	0	Moderate	0	8-27	Endothelium dependent NO-mediated vasodilation

ISA, intrinsic sympathomimetic activity; IV, intravenous; MSA, membrane-stabilizing activity; NA, not applicable; NO, nitric oxide.
Adapted from Mason et al.,[3] Manrique et al.,[18] and Frishman.[22]

Canadian Journal of Cardiology 28 (2012) 334–340

Review

The Evolving Role of β-Adrenergic Receptor Blockers in Managing Hypertension

Luc Poirier, BPharm, MSc, and Yves Lacourcière, MD, FRCPC, FACP

Unité d'hypertension, Centre de recherche, Centre Hospitalier Universitaire de Québec, Québec, Québec, Canada

- Yıllardır beta blokörler hipertansiyon tedavisinde kullanılmakta ve belirgin bir şekilde etkilidirler.
- Ayrıca birçok metaanaliz özellikle 60 yaş altındaki hastalarda kullanıldığında kardiyovasküler olaylar üzerine olumlu etkileri olduğunu göstermiştir.
- Ancak konvansiyonel betablokörlerin özellikle kalp hızı ve kardiyak output üzerine etkileri daha belirgin olduğu için hipertansiyon tedavisinde seçilecek en uygun ajan olmayabilirler.

Canadian Journal of Cardiology 28 (2012) 334–340

Review

The Evolving Role of β-Adrenergic Receptor Blockers in Managing Hypertension

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Unité d'hypertension, Centre de recherche, Centre Hospitalier Universitaire de Québec, Québec, Québec, Canada

- Son zamanlarda vazodilatasyon özelliği olan 3. kuşak beta blokörler üzerine çok çalışma yapılmıştır.
- Sonuç olarak Kanada Hipertansiyon Eğitim Programına (CHEP) göre Beta Blokörler kalp yetmezliği ve MI hikayesi olan hastalar ve 60 yaş altındaki tüm hipertansif hastalar için hipertansiyon tedavisinde ilk seçenektirler.

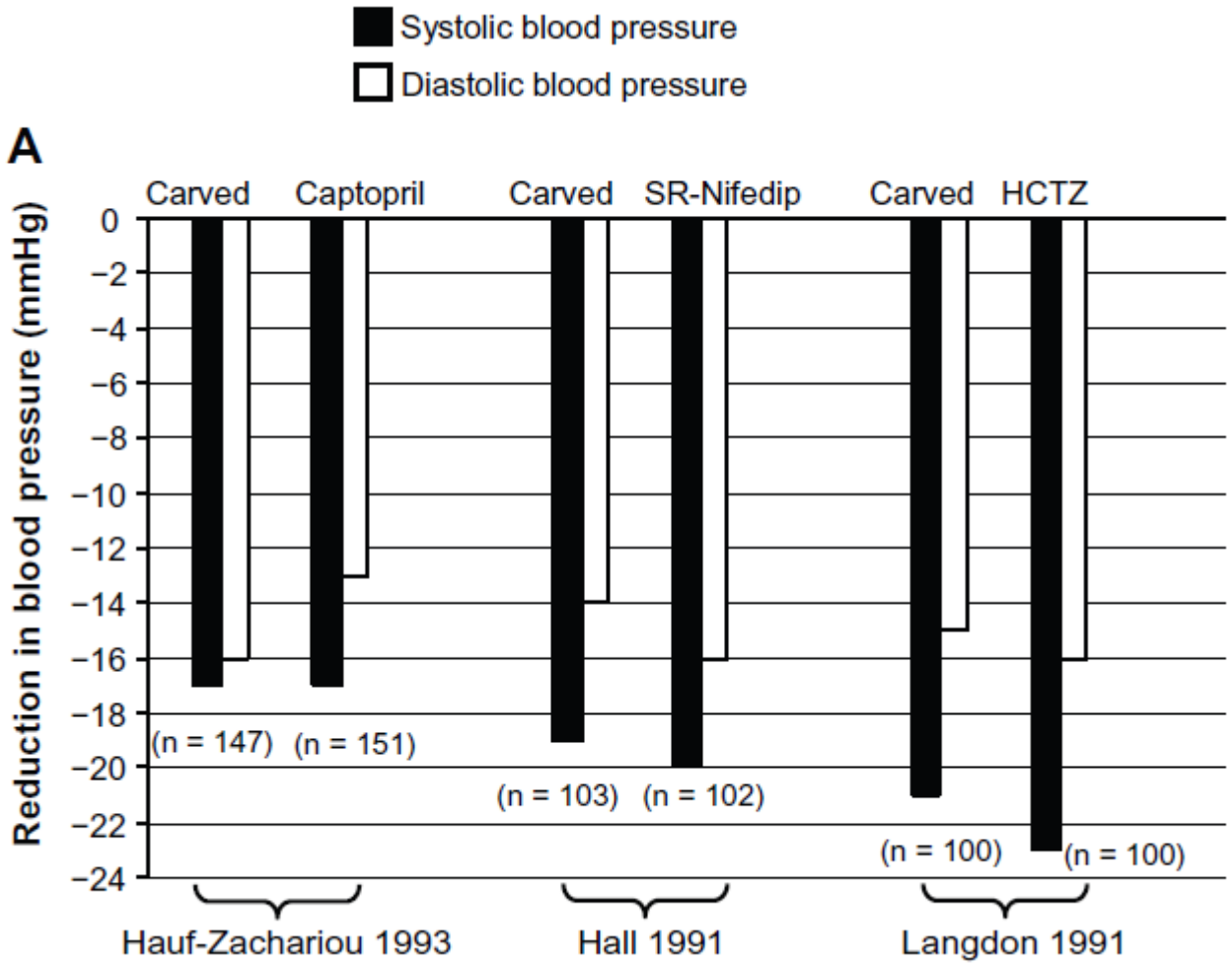
Use of carvedilol in hypertension: an update

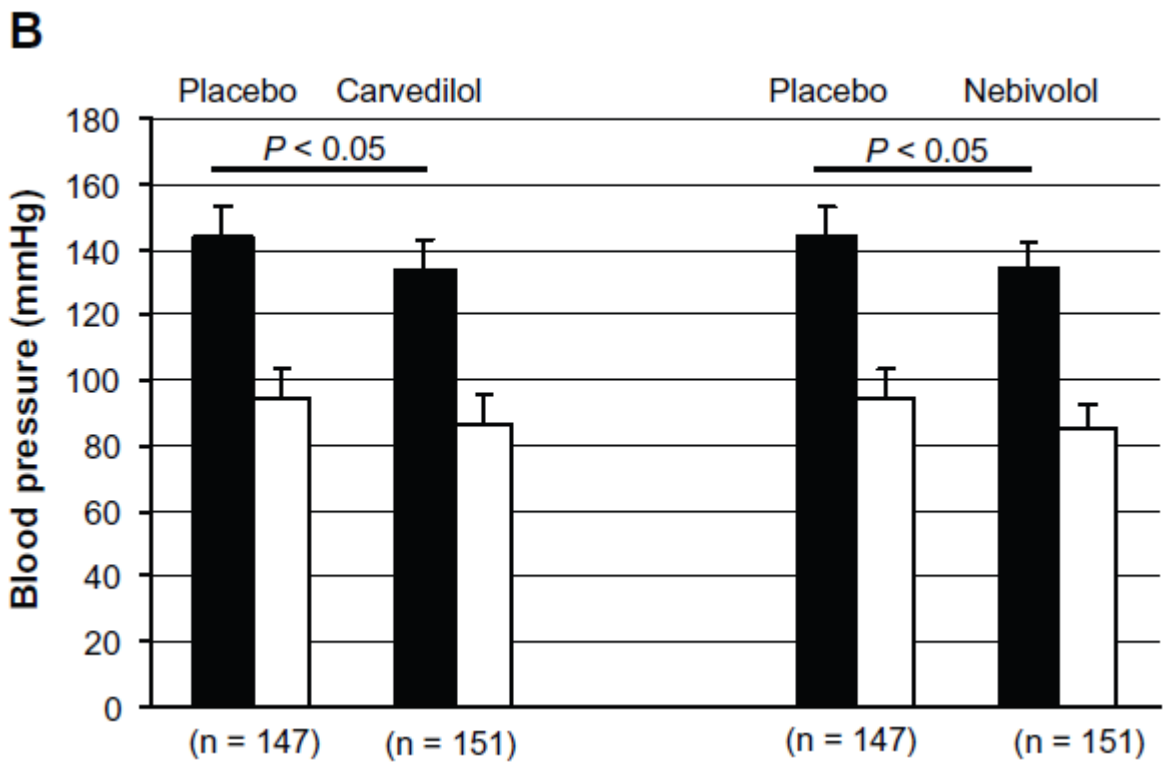
Table 1 Effects of different antihypertensive drugs in hypertensive patients

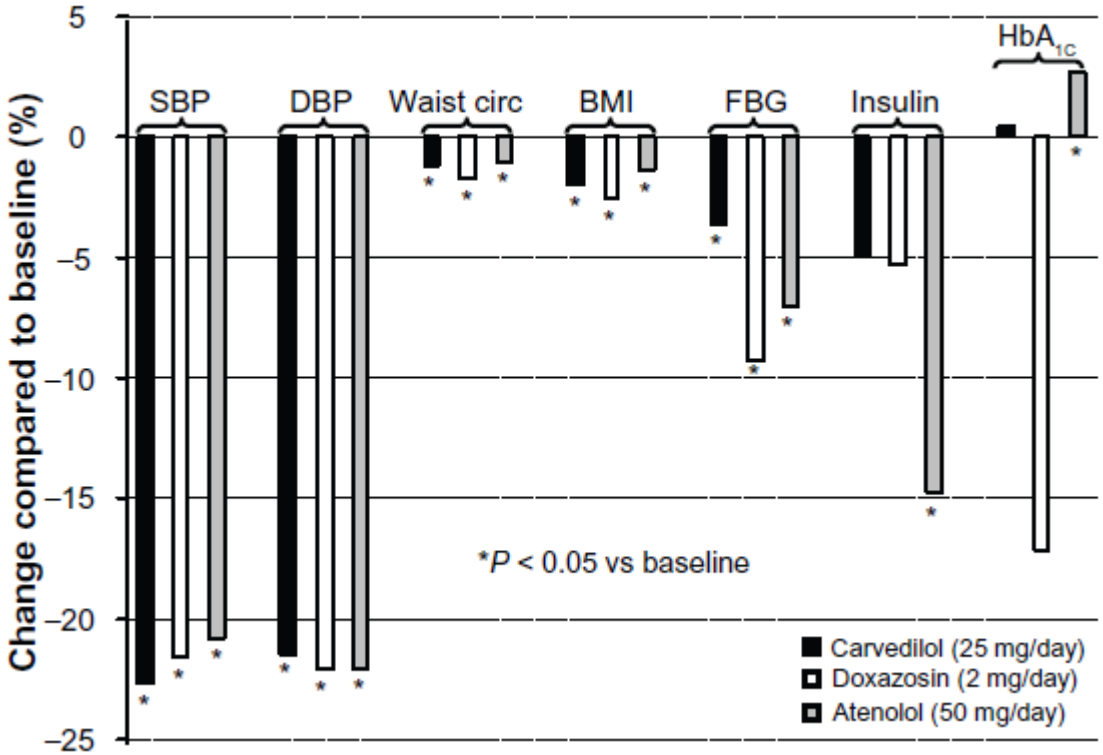
Parameter	Ideal drug	ACEI or ARB	Carvedilol	α1-adrenoceptor blocker	DHP calcium antagonist	Traditional β-blockers	Thiazide diuretic
MAP	↓	↓	↓	↓	↓	↓	↓
TPR	↓	↓	(↓)	↓	↓	(↑)	↓
Cardiac output	0	0	0	0	0	(↓)	0
Heart rate	0/↓	0	↓	(↑)	(↑)	↓	0
SNS activation	↓	↓	↓	(↑)	↑	↓	↑
RAS	↓	↓	↓	0	↑	↓	↑
Lipid metabolism	0/+	0/+	0	0/+	0	–	–
Glucose metabolism	0/+	0	0	0	0	–	–

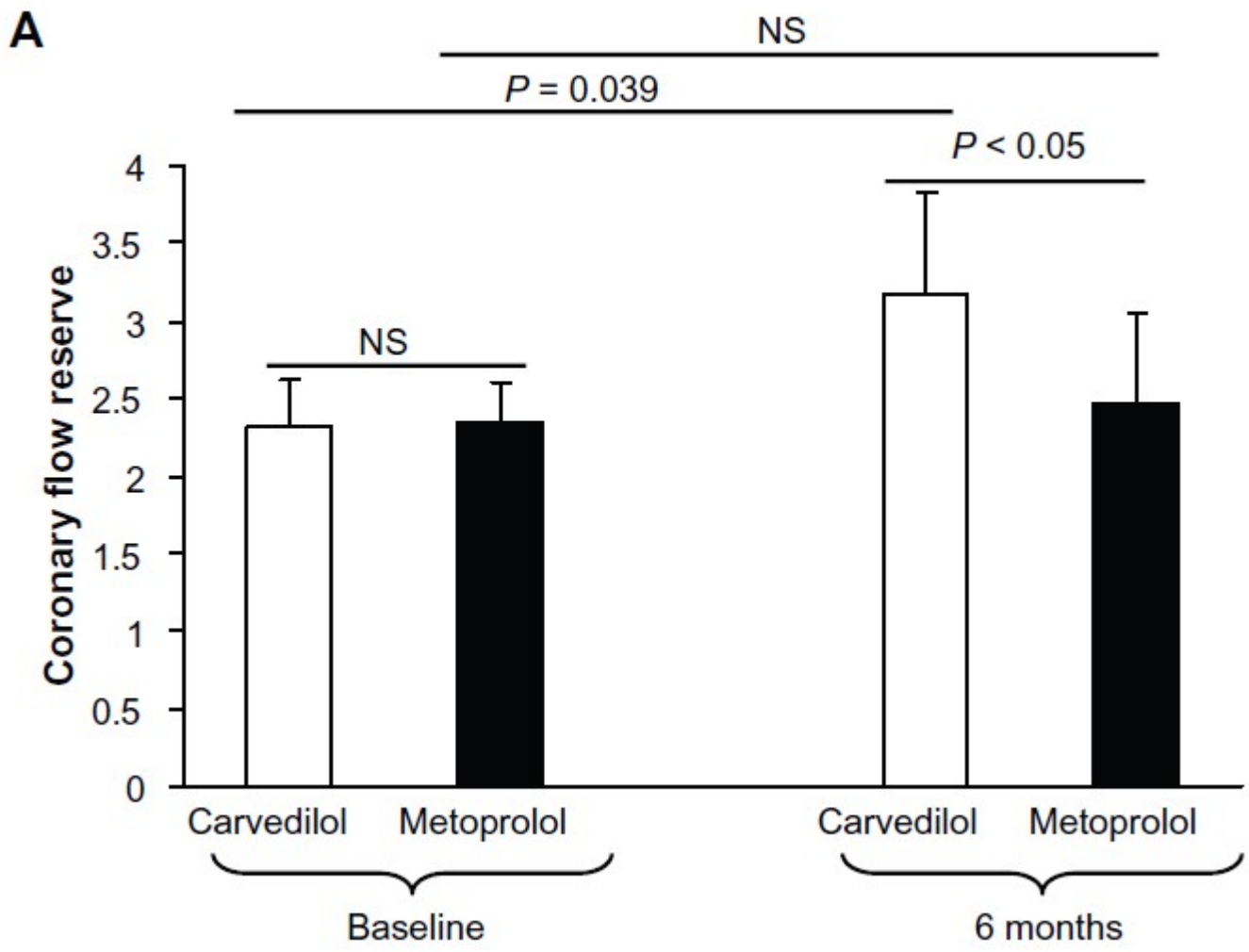
Notes: Effects are color-coded where white represents positive effect whereas black represents negative effects and light grey and dark grey represent slight positive and slight negative effects respectively. Data drawn from Messerli FH, Grossman E. Beta-blockers in hypertension: is carvedilol different? *Am J Cardiol.* 2004;93 Suppl:7B–12B.[9]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP, dihydropyridine; MAP, mean arterial blood pressure; SNS, sympathetic nervous system; RAS, renin-angiotensin system; TPR, total peripheral resistance; ↑, increase (activation); ↓, decrease (inhibition); 0, no effect; +, positive effect; -, negative effect; ( ), predominantly after acute administration.


Systolic blood pressure
Diastolic blood pressure
A
Carved
Captopril
Carved
SR-Nifedip
Carved
HCTZ
Reduction in blood pressure (mmHg)
0
−2
−4
−6
−8
−10
−12
−14
−16
−18
−20
−22
−24
(n = 147)
(n = 151)
(n = 103)
(n = 102)
(n = 100)
(n = 100)
Hauf-Zachariou 1993
Hall 1991
Langdon 1991


B
Placebo
Carvedilol
Placebo
Nebivolol
P < 0.05
P < 0.05
Blood pressure (mmHg)
180
160
140
120
100
80
60
40
20
0
(n = 147)
(n = 151)
(n = 147)
(n = 151)


Change compared to baseline (%)
5
0
–5
–10
–15
–20
–25
SBP
DBP
Waist circ
BMI
FBG
Insulin
HbA1c
*P < 0.05 vs baseline
Carvedilol (25 mg/day)
Doxazosin (2 mg/day)
Atenolol (50 mg/day)


A
NS
P = 0.039
P < 0.05
NS
Coronary flow reserve
4
3.5
3
2.5
2
1.5
1
0.5
0
Carvedilol
Metoprolol
Carvedilol
Metoprolol
Baseline
6 months

Use of carvedilol in hypertension: an update

Vascular Health and Risk Management

- JNC-7 klavuzuna göre carvedilol gibi betablokörler kardiyak risk faktörü olan veya olmayan stage 1 hipertansiyonu olan hastalarda ilk seçenek ilaç olarak önerilmektedir.
- Stage 2 hipertansiyonlu hastalarda da kombinasyonda ilk seçenek olarak önerilmektedir.
- Özellikle Carvedilol'ün hemodinamik ve metabolik yararlı etkilerini daha ayrıntılı bir şekilde ortaya koymak için böbrek ve periferik vasküler hastalıkları gibi durumları olan spesifik hasta grupları ile randomize kontrollü çalışmalara ihtiyaç vardır.

ht_update2011.pdf - Adobe Reader

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Hypertensive emergencies: an update

Paul E. Marik[a] and Racquel Rivera[b]

[a]Department of Medicine, Eastern Virginia Medical School and [b]Department of Pharmacy, Sentara Norfolk General Hospital, Norfolk, Virginia, USA

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E-mail: marikpe@evms.edu

Current Opinion in Critical Care 2011, 17:569–580

Purpose of review

Systemic hypertension (HTN) is a common medical condition affecting over 1 billion people worldwide. One to two percent of patients with HTN develop acute elevations of blood pressure (hypertensive crises) that require medical treatment. However, only patients with true hypertensive emergencies require the immediate and controlled reduction of blood pressure with an intravenous antihypertensive agent.

Recent findings

Although the mortality from hypertensive emergencies has decreased, the prevalence and demographics of this disorder have not changed over the last 4 decades. Clinical experience and reported data suggest that patients with hypertensive urgencies are frequently inappropriately treated with intravenous antihypertensive agents, whereas patients with true hypertensive emergencies are overtreated with significant complications.

Summary

Despite published guidelines, most patients with hypertensive crises are poorly managed with potentially severe outcomes.

Keywords

aortic dissection, clevidipine, eclampsia, esmolol, hypertension, hypertensive emergencies, labetalol, nicardipine, pulmonary edema

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Hypertensive emergencies: an update

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Table 1 Recommended antihypertensive agents for hypertensive crises

Condition	Preferred antihypertensive agent
Acute pulmonary edema – systolic dysfunction	Nicardipine or clevidipine in combination with nitroglycerin and a loop diuretic
Acute pulmonary edema – diastolic dysfunction	Esmolol, metoprolol, labetalol or verapamil in combination with low-dose nitroglycerin and a loop diuretic
Acute myocardial ischemia	Labetalol or esmolol in combination with nitroglycerin
Hypertensive encephalopathy	Nicardipine, clevidipine or labetalol
Acute aortic dissection	Labetalol or combination of nicardipine/clevidipine and esmolol or combination of nitroprusside with either esmolol or intravenous metoprolol
Preeclampsia, eclampsia (SBP >150 mmHg)	Labetalol or nicardipine
Acute renal failure/microangiopathic anemia	Nicardipine, clevidipine or fenoldopam
Sympathetic crisis/cocaine overdose	Verapamil, diltiazem, nicardipine or clevidipine in combination with benzodiazepine
Acute postoperative hypertension	Esmolol, clevidipine, nicardipine or labetalol
Ischemic stroke (SBP >180–200 mmHg)	Nicardipine, clevidipine or labetalol
Hemorrhagic stroke (SBP >140–160 mmHg)	Nicardipine, clevidipine or labetalol

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TR 14:49 05.04.2012

Curr Opin Crit Care 17:569–580
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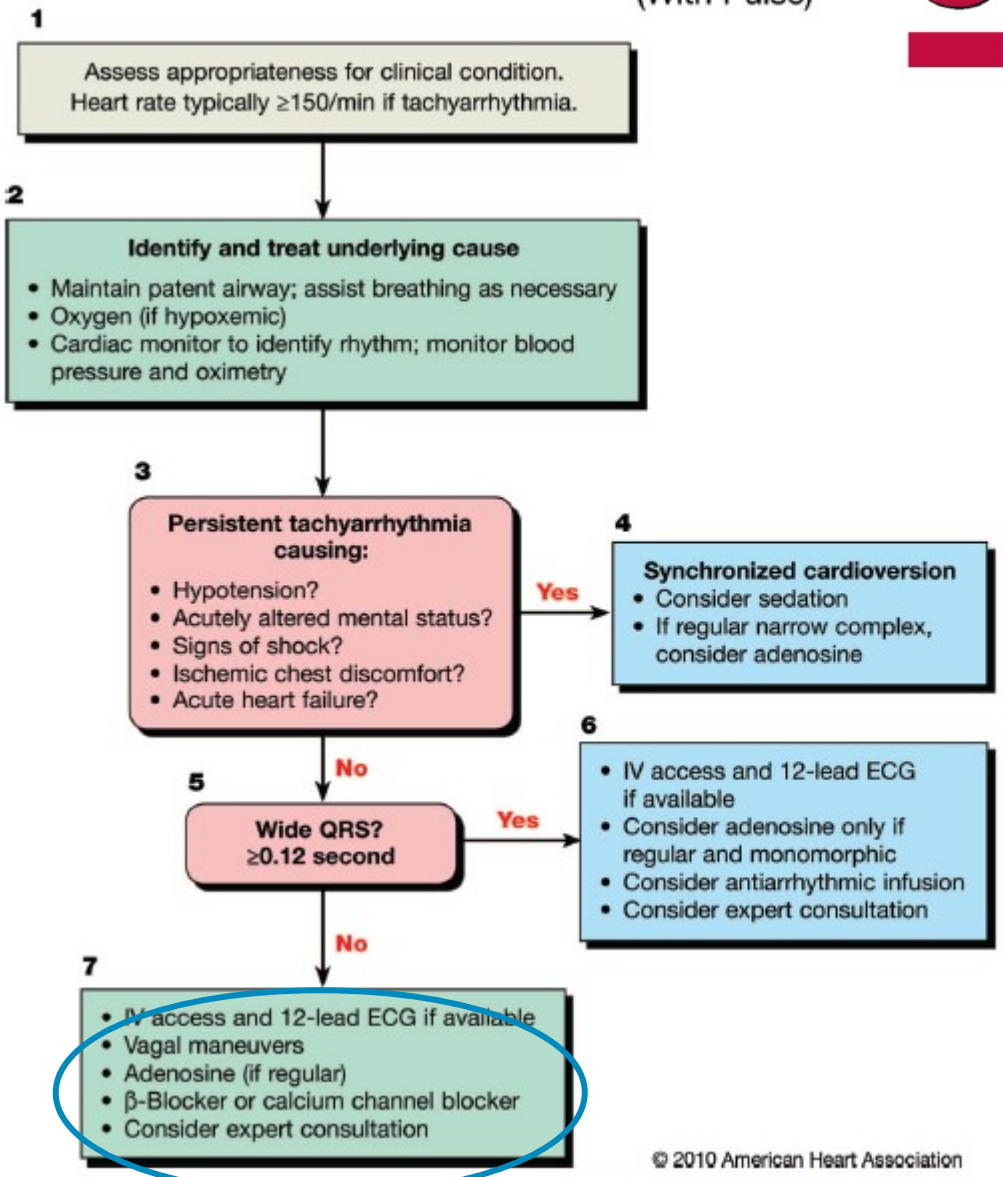
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Adult Tachycardia
(With Pulse)



Doses/Details

Synchronized Cardioversion
Initial recommended doses:
- Narrow regular: 50-100 J
- Narrow irregular: 120-200 J biphasic or 200 J monophasic
- Wide regular: 100 J
- Wide irregular: defibrillation dose (NOT synchronized)

Adenosine IV Dose:
First dose: 6 mg rapid IV push; follow with NS flush.
Second dose: 12 mg if required.

Antiarrhythmic Infusions for Stable Wide-QRS Tachycardia

Procainamide IV Dose:
20-50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases >50%, or maximum dose 17 mg/kg given.
Maintenance infusion: 1-4 mg/min.
Avoid if prolonged QT or CHF.

Amiodarone IV Dose:
First dose: 150 mg over 10 minutes.
Repeat as needed if VT recurs.
Follow by maintenance infusion of 1 mg/min for first 6 hours.

Sotalol IV Dose:
100 mg (1.5 mg/kg) over 5 minutes.
Avoid if prolonged QT.

Figure 4. Tachycardia Algorithm.

(*Circulation*. 2010;122[suppl 3]:S729–S767.)
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Esmolol

A Review of its Use in the Short-Term Treatment of Tachyarrhythmias and the Short-Term Control of Tachycardia and Hypertension

Study	Treatment[a]	No. of pts	Response (% of pts)			
			Overall[b]	NSR	HR ↓ by ≥20%	HR <100 bpm
Versus PL						
Anderson et al.[35]	ESM	32/35[c]	72*/89[c]	6/6[c]		
	PL	31/2[c]	6/NR[c]	NR/NR[c]		
Versus active comparator drugs						
Abrams et al.[36]	ESM	50/30[c]	72/67[c]	14/27[c]	64/67[c]	32/43[c]
	PRO	55/36[c]	69/58[c]	16/31[c]	69/50[c]	34/42[c]
Balser et al.[37]	ESM[d]	34/26[e]		59*[f]/85[e]		
	DIL[d]	30/26[e]		33[f]/62[e]		
As concomitant treatment						
Fragakis et al.[38]	ESM + IBU[g]	44		67‡		
	IBU[g]	46		46		

Drugs 2012; 72 (1): 109-132
0012-6667/12/0001-0109/$55.55/0

Original Article

Guidelines for the diagnosis and management of Catecholaminergic Polymorphic Ventricular Tachycardia

Andreas Pflaumer, MD[a,b,*] and Andrew M. Davis, MD[a,b,c]

[a] *The Royal Children's Hospital Melbourne, Australia*
[b] *University of Melbourne, Australia*
[c] *The Murdoch Children's Research Institute, Australia*

Background: **Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited arrhythmia syndrome, characterised by polymorphic ventricular tachycardia induced by adrenergic stress. CPVT can be caused by mutations the cardiac ryanodine receptor gene (*RYR2*) or mutations in the cardiac calsequestrin gene *CASQ2*. Structural heart disease is usually absent and the baseline ECG is usually normal. Patients with CPVT often present with exercise- or emotion induced syncope, the first presentation can also be sudden cardiac death.**

Management: **Besides removal of triggers treatment with beta blockers is currently a class I indication in clinically diagnosed patients. Beta blockage should be titrated up to an effective level. The addition of flecainide seems to be a promising approach in patients where arrhythmias are not completely suppressed by beta blockers. A cardioverter-defibrillator (ICD) or left cervical sympathetic denervation might be considered under special circumstances. Genetic counselling is recommended and all first degree relatives should be properly evaluated.**

(Heart, Lung and Circulation 2012;21:96–100)

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Keywords. Catecholaminergic Polymorphic Ventricular Tachycardia; CPVT; Guidelines; Sudden death; Diagnosis; Management; Bidirectional ventricular tachycardia; Genetics; Calsequestrin; Ryanodine

Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: A systematic review

Cammarata et al.[29]	Sprague-Dawley rats	6 min after VF	8 min after VF	(a) Placebo (b) Esmolol (300 μg/kg)	ROSC – Survival (h) – Number of shocks 5/9 – 20 ± 11 – 14 ± 6 9/9 – 50 ± 25 – 7 ± 4 OBS: No exogenous epinephrine administration in either group. Better postresuscitation contractile and lusinotropic in group (b)	
Huang[32]	Sprague-Dawley rats	8 min after VF	Carvedilol (50 μg/kg) – 15 min before VF Epinephrine (30 μg/kg) – 10 min after VF	(a) Placebo + Placebo (b) Placebo + Epinephrine (c) Carvedilol + Epinephrine (d) Carvedilol + Placebo	Group (c) treatment reduced ventricular ectopy and minimized increases in arterial blood lactate at 5 min after ROSC, with longer post-resuscitation survival and less neurological deficit	Equivalent increases in coronary perfusion pressure were observed after the injection of epinephrine independently of carvedilol pretreatment
Bassiakou et al.[31]	Landrace/Large White piglets	8 min after VF	8 min after VF	(a) Epinephrine (0.02 mg/kg) (b) Atenolol (0.05 mg/kg) + Epinephrine (0.02 mg/kg)	ROSC – PVC[a] – VF recurrence 4/10 – 85 ± 30 – 18 ± 6 9/10 – 40 ± 27 – 2 ± 1 OBS: HR in group (a) > group (b) (in the first 10 min postresuscitation)	
Jingjun et al.[28]	Yorkshire-cross domestic pigs	4 min after VF	8 min after VF	(a) Placebo (b) Esmolol (0.5 mg/kg)	ROSC – Number of shocks – VF recurrence 18/20 – 3.5 ± 2.5 – 5/18 17/20 – 1.5 ± 0.5 – 0/17 OBS: All animals received epinephrine at 4 and 5 min after VF Animals were randomized to drug treatments only after failure of the first defibrillation attempt (at 6 min) Lower HR, BP, and CPP were seen within 30 min post-resuscitation in group (b) Also realized other important in vitro experiments	

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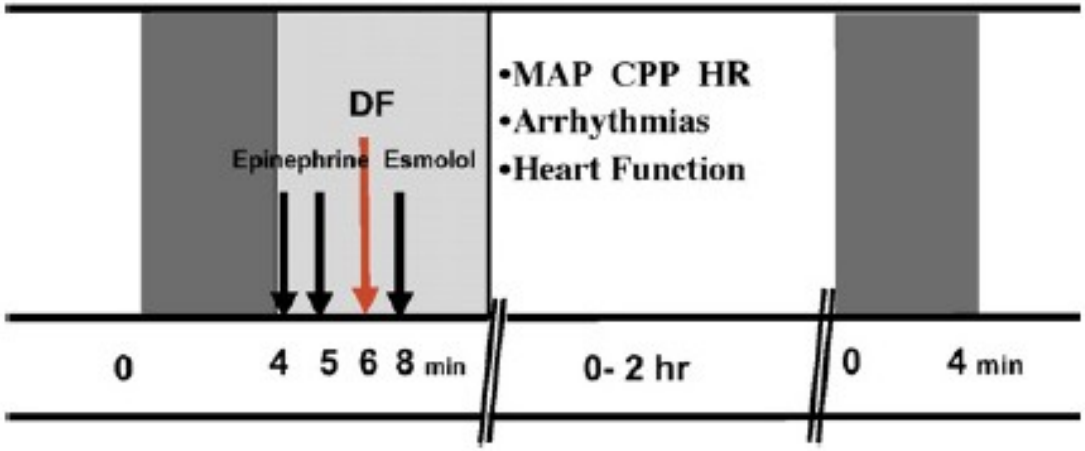
Experimental paper

Effect and mechanism of esmolol given during cardiopulmonary resuscitation in a porcine ventricular fibrillation model☆

Experimental Protocol



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significantly reduced the onset and maintenance of VF.

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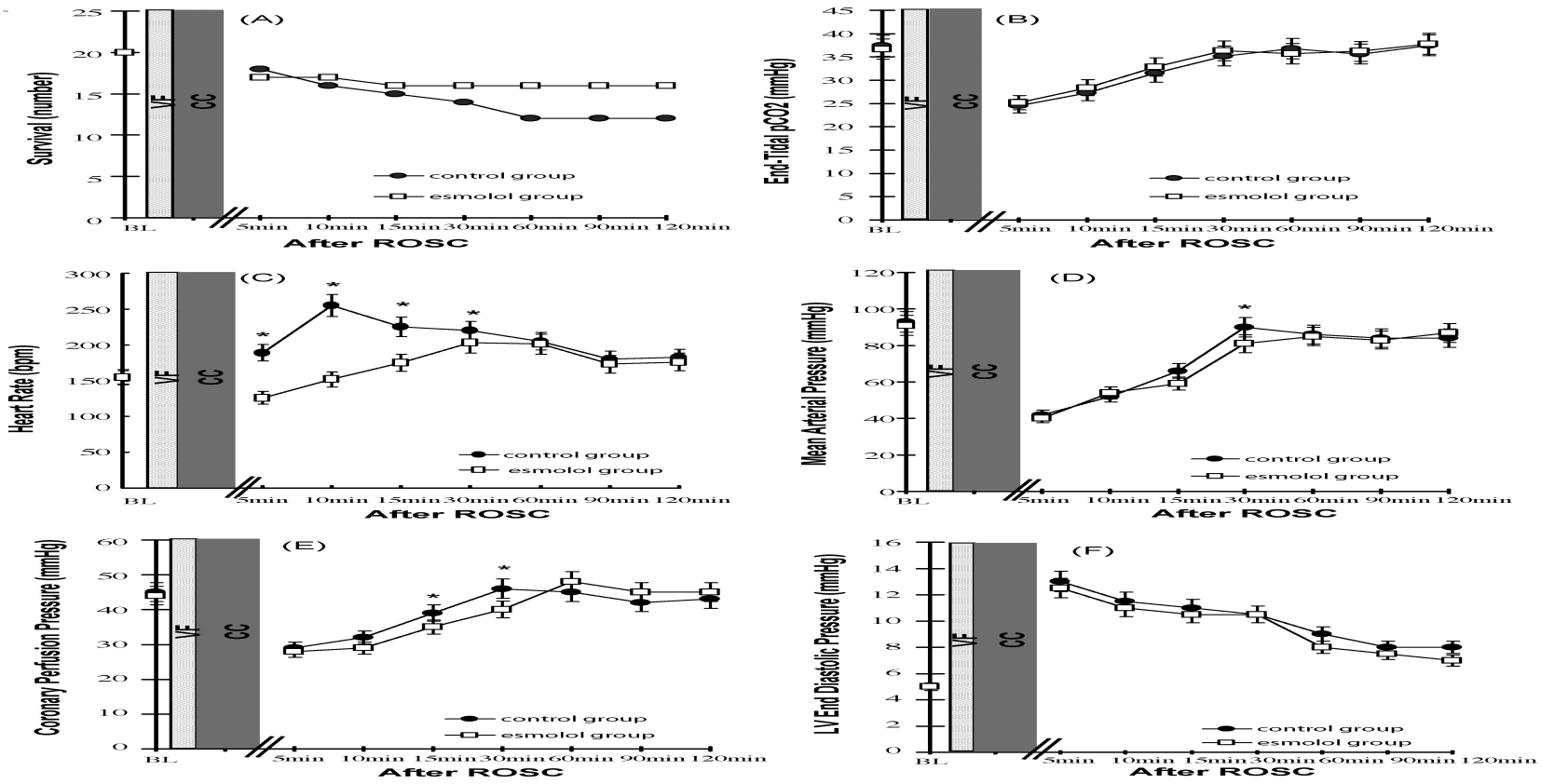
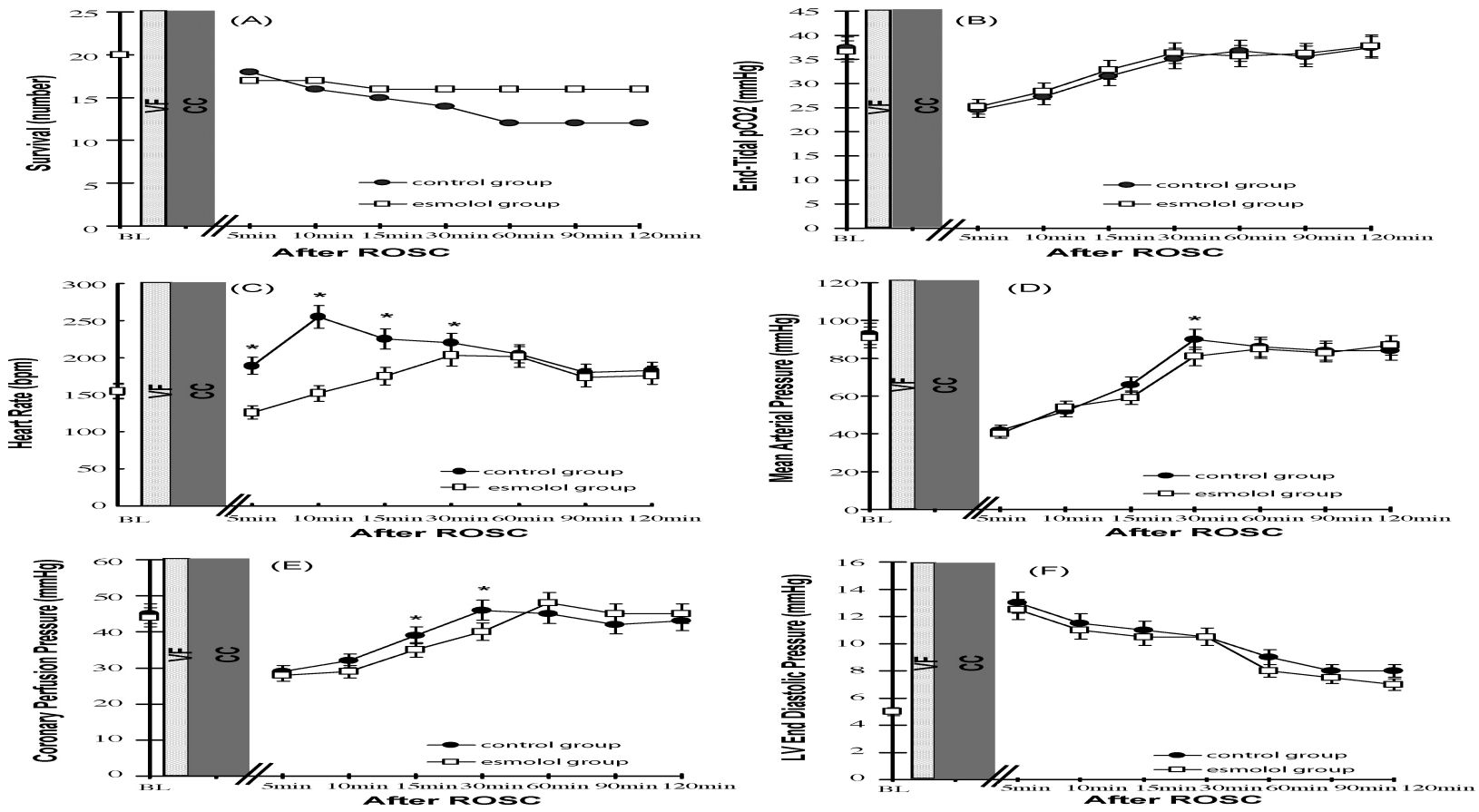
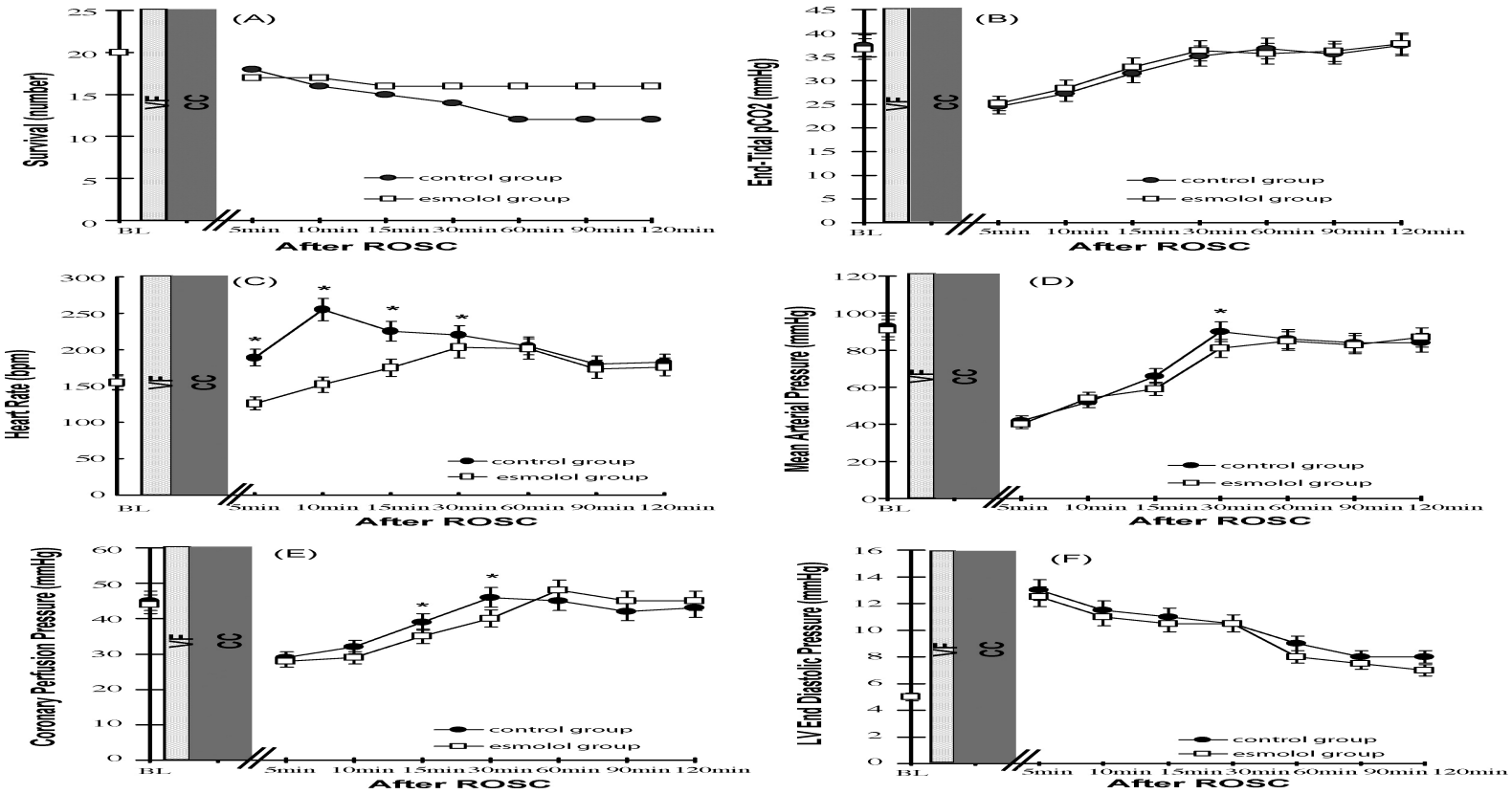


Resuscitation 80 (2009) 1052–1059



Resuscitation 80 (2009) 1052–1059



Resuscitation 80 (2009) 1052–1059

Review article

Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: A systematic review

Felipe Ca[illegible]s Ritt[b,c]

Case reports.

Author	Population size	Age median	β-Blocker	Results	Notes
Besterman[36,a]	n = 1	60	Propranolol (60 mg)	The Adams–Stokes attacks diminished in frequency and finally ceased	The first 10 mg were given IV
Sloman[37]	n = 3	44	Propranolol (15–22 mg)	VF ceased in all cases, but 2 patients died: – One developed circulatory failure because VF episodes recurred for 30 h before propranolol administration and consequent VF termination – The other evolved with hypoxemia and asystole after VF termination by propranolol; she had heart failure	Except for the patient with heart failure, the other two had had a recent myocardial infarction
Iwatsuki[38]	n = 1	22	Propranolol (4 mg)	Propranolol 4 mg given intravenously completely suppressed the recurrent attacks after other drugs had failed.	The patient was suspected to have a certain localized myocarditis that triggered the VF episodes.
Ikram[39]	n = 4	58	Propranolol (1 mg)	Successful control of persistent ventricular fibrillation in all 4 patients.	Except for a 73 years old lady, with massive LV MI, all patients survived to hospital discharge
Rothfeld[40]	n = 1	64	Propranolol (5 mg)	The patient survived to discharged; He had had a MI that evolved with recurrent VF Propranolol reverted to sinus rhythm after large doses of lidocaine and procainamide had failed	Propranolol was administered immediately after sinus rhythm was restored by a direct current electric shock
Mason[41]	n = 3	59	Propranolol (2–5 mg)	Successful termination of VF and survival to hospital discharge 2 patients had a MI preceding the VF episodes	Propranolol was used after lidocaine and procainamide had failed to revert VF
Van Dantzig[42]	n = 1	23	Esmolol (500 μg/kg)	Complex ectopic ventricular activity was completely suppressed together with a reduction in heart rate and a significant decrease of ST segment elevation. The patient survived to discharge	The patient had a acute transmural anteroseptal ischemia after a cardiac surgery
Schmidt[43]	n = 1	18	Metoprolol (5 mg)	The patient responded almost immediately with resolution of the VF and no recurrence The patient survived to discharge with no further complications	Electrical storm occurred after liver transplant for fulminant Wilson's disease
Srivatsa[44,a]	n = 1	20	Esmolol	The VF episodes ceased immediately after esmolol administration. The patient survived to discharge and referred to psychiatric care	The episodes were precipitated by synephrine overdose
Tsagalou[45]	n = 1	60	Propranolol (0.5 mg)	VF immediately subsided and was replaced by a ventricular paced rhythm	The therapeutic effect of propranolol was not sustained in absence of amiodarone (after hospital discharge)

[illegible]012) 674–683

Review article

Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: A systematic review

Felipe Carvalho de Oliveira[a,b], Gilson Soares Feitosa-Filho[a,b,*], Luiz Eduardo Fonteles Ritt[b,c]

Human studies.

Author	Population	Groups	β-Blockade Strategy	Results	Notes
Nademanee[34]	49 post-MI patients	(1) ACLS-guided therapy ($n=22$) (2) Adrenergic Blockade ($n=27$)	LSGB ($n=6$) Esmolol ($n=7$) Propranolol ($n=14$)	Significant reduction in VF episodes Better short term (82% vs. 22%) and long term survival (66% vs. 4%) in the adrenergic-blockade group	Patients were assigned to each treatment arm according to physician preference, rather than randomly assigned
Miwa[35]	42 consecutive ES patients	All patients received β-blockade after failure of ACLS-guided therapy	Landiolol in increasing doses (up to arrhythmia control)	Overall survival was 60% Landiolol was ineffective in arrhythmia control in 9 patients	Both responders and survivors had lower age and APACHE II scores compared to non-responders and non-survivors

Review article

Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: A systematic review

Felipe Carvalho de Oliveira[a,b], Gilson Soares Feitosa-Filho[a,b,*], Luiz Eduardo Fonteles Ritt[b,c]

·Prospektif insan çalışmaları her nekadar VF veya NVT ye bağlı kardiyak arrestlerde beta blokör tedavisinin etkili olduğunu gösterse da daha kaliteli insan çalışmalarına gereksinim vardır.

Resuscitation 83 (2012) 674–683

β-BLOCKERS IN SEPSIS: REEXAMINING THE EVIDENCE

Nathan M. Novotny,* Tim Lahm,† Troy A. Markel,* Paul R. Crisostomo,* Meijing Wang,* Yue Wang,* Rinki Ray,* Jiangning Tan,* Dalia Al-Azzawi,* and Daniel R. Meldrum*‡§

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·Sepsis gibi hipotansiyona sebep olabilecek durumda bilinen hipotansif etkisi olan bir ilacın kullanımı ilk bakışta mantıksız gibi görünse de beta blokörlerin metabolizma ve immunomodülatuvar etkileri sayesinde tedavide faydalı olabileceği düşünülmektedir.

·Ancak bu konuda hayvan ve insan çalışmaları yeterli sayıda değildir.

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heart failure, and arterial hypertension. Recent data suggest that β-blocker effects on metabolism, glucose homeostasis, cytokine expression, and myocardial function may be beneficial in the setting of sepsis. Although treating a potentially hypotensive condition with a drug with antihypertensive properties may initially seem counterintuitive, the metabolic and immunomodulatory properties of β-blockers may be of benefit. It is the purpose of this review to discuss the effects of β-blockers on the following: (1) metabolism, (2) glucose regulation, (3) the inflammatory response, (4) cardiac function, and (5) mortality in sepsis.

KEYWORDS—Propranolol, esmolol, LPS, shock, β-adrenergic receptor, endotoxin, cytokines

Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis*

Alejandro Macchia, MD; Marilena Romero, PhD; Pablo Dino Comignani, MD; Javier Mariani, MD; Antonio D'Ettorre, PhD; Nadia Prini, MD; Mariano Santopinto, MD; Gianni Tognoni, MD

Table 1. Demographic and clinical characteristics of the study population

Variable	All Patients	β-Blockers	No β-Blockers	*p*
N (%)	9465 (100)	1061 (11.2)	8404 (88.8)	
Demographic and baseline conditions				
Male, n (%)	4565 (49.6)	522 (49.2)	4186 (49.8)	.720
Age, mean (SD)	72.0 (12.8)	72.0 (10.6)	72.0 (13.0)	.961
Hypertension, n (%)	4880 (51.6)	862 (81.2)	4018 (47.8)	<.001
Dyslipemia, n (%)	1039 (11.0)	293 (28.2)	746 (8.9)	<.001
Diabetes, n (%)	2321 (24.5)	343 (32.3)	1978 (23.5)	<.001
Prior congestive heart failure, n (%)	1771 (18.7)	438 (41.3)	1333 (15.9)	<.001
Prior atrial fibrillation, n (%)	602 (6.4)	129 (12.2)	473 (5.6)	<.001
Prior myocardial infarction, n (%)	107 (1.1)	43 (4.1)	64 (0.8)	<.001
Chronic obstructive pulmonary disease, n (%)	1522 (16.1)	157 (14.8)	1365 (16.2)	.249
Depression, n (%)	990 (10.5)	140 (13.2)	850 (10.1)	.003
Malignancy, n (%)	1947 (20.6)	194 (18.3)	1753 (20.9)	.053
In-hospital characteristics and severity				
No organ dysfunction	6970 (73.6)	734 (69.2)	6236 (74.2)	.001
One organ dysfunction	2140 (22.6)	295 (27.8)	1845 (22.0)	<.001
Two organ dysfunction	308 (3.3)	28 (2.6)	280 (3.3)	.23
≥3 organ dysfunction	47 (0.5)	4 (0.4)	40 (0.5)	.56

Crit Care Med 2012 Vol. 40, No. 10

Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis*

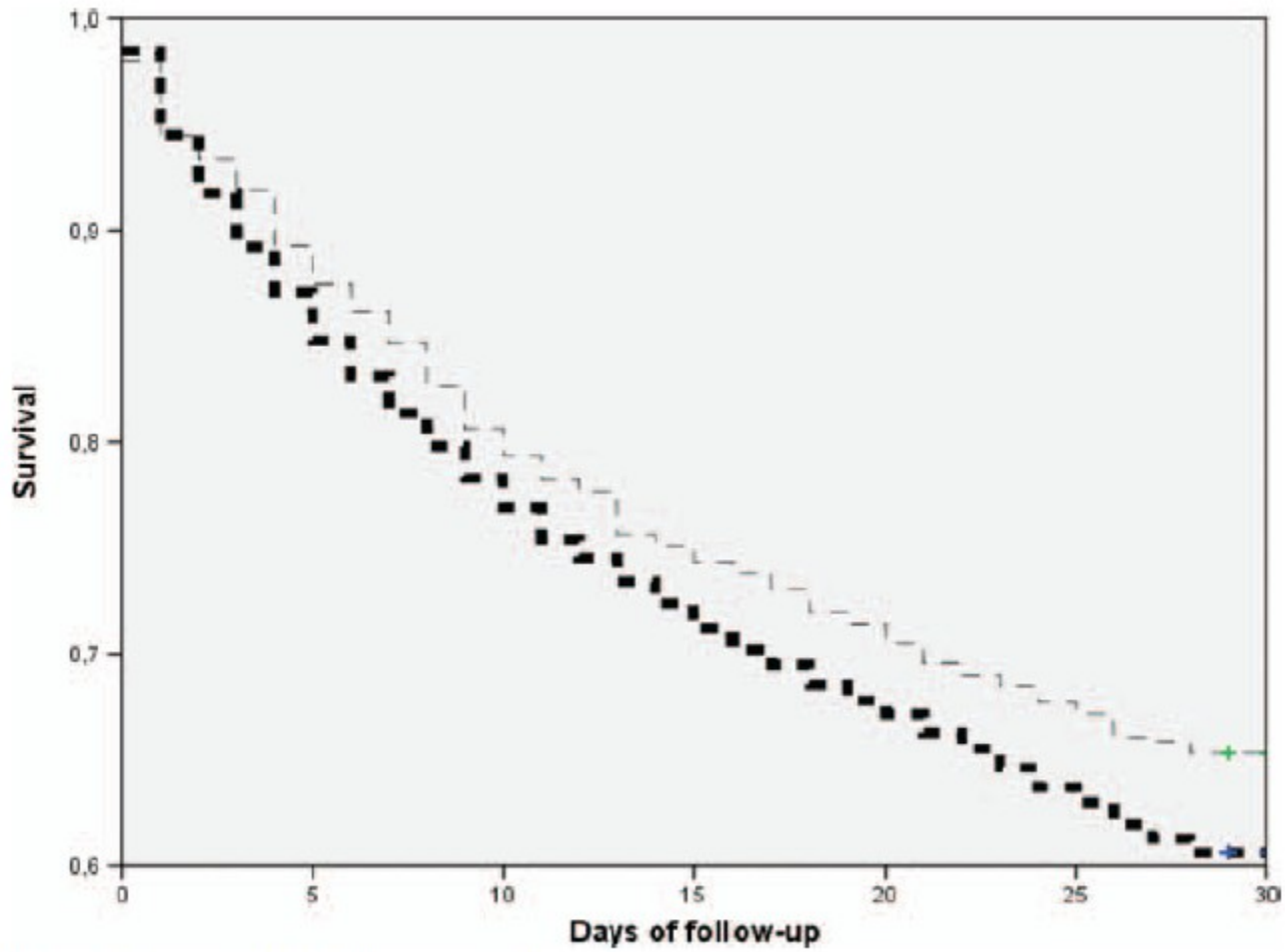

Figure 1. Survival plot for 28-day mortality.

Sympathetic Hyperactivity After Traumatic Brain Injury and the Role of Beta-Blocker Therapy

Daithi S. Heffernan, MD, Kenji Inaba, MD, Saman Arbabi, MD, MPH, and Bryan A. Cotton, MD, MPH

TABLE 2. Retrospective Studies Linking the Association Between Beta-Blocker Use in Patients With Traumatic Brain Injury and Improved Survival

Authors	Inclusion Criteria	BB (−) Patients (n)	BB (+) Patients (n)	Mortality in BB (−) Patients, n (%)	Mortality in BB (+) Patients, n (%)	*p*
Arbabi et al.[74]	GCS <13	511	94	163 (32)	17 (18)	<0.001
Cotton et al.[73]	Head AIS ≥3	246	174	27 (11)	9 (5.2)	0.03
Riordan et al.[84]	Head AIS ≥5	308	138	135 (44)	29 (21)	<0.001
Salim et al.[89]	Head AIS >3	329	91	118 (36)	22 (24)	0.03
Inaba et al.[75]	CHI with ICU admission	953	203	199 (21)	34 (17)	0.01
Neideen et al.[76]	Any pretrauma beta-blocker use	463	105	161 (13.4)	40 (14.7%)	0.558

AIS, Abbreviated Injury Scale; BB, beta-blocker; CHI: Closed Head Injury; GCS: Glasgow Coma Scale.
All the studies denote similar improvements in mortality associated with beta-blockers, despite these patients being older and, in general, more severely injured.

Sympathetic Hyperactivity After Traumatic Brain Injury and the Role of Beta-Blocker Therapy

Daithi S. Heffernan, MD, Kenji Inaba, MD, Saman Arbabi, MD, MPH, and Bryan A. Cotton, MD, MPH

- Sağkalım beklentisi olmayan kafa travmaları dışında ölüm nedeni öncelikle kardiyak nedenler olmak üzere sinir sistemi dışındaki organların disfonksiyonuna bağlıdır.
- Paroksismal sempatik storm olarak adlandırılan durum hipotalamik bozukluk veya beyindeki eksitatör-inhibitör dengesinin bozulması sonucu ortaya çıkan bir tablodur.
- Beta blokörler ile hiperadrenerjik cevabın baskılanması sonucu özellikle yaşlılar ve daha ciddi travması olan hastaların mortalitesinde belirgin azalma görülmüştür.
- Ancak doz ayarı, veriliş şekli ve zamanı, hangi ajanın kullanılacağı gibi soruların cevabı halen net değildir.

The Journal of **TRAUMA**® *Injury, Infection, and Critical Care* • Volume 69, Number 6, December 2010

Sympathetic Hyperactivity After Traumatic Brain Injury and the Role of Beta-Blocker Therapy

Daithi S. Heffernan, MD, Kenji Inaba, MD, Saman Arbabi, MD, MPH, and Bryan A. Cotton, MD, MPH

- Yapılan hayvansal deneylerde ağır kafa travmalı deneklerde esmolol infüzyonunun kardiyak fonksiyonları koruduğu ve bu sayede diğer organ fonksiyonlarının da korunduğu tespit edilmiştir.
- Bu sayede travma sonrası potansiyel organ donörlerinde esmolol uygulanarak organ canlılığının daha uzun süre korunması mümkün olabilecek gibi görülmektedir.

The Journal of **TRAUMA**® *Injury, Infection, and Critical Care* • Volume 69, Number 6, December 2010

Meta-analysis: beta-blockers versus banding ligation for primary prophylaxis of esophageal variceal bleeding

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ABSTRACT

Aim. To perform an updated meta-analysis comparing β-blockers (BB) with endoscopic variceal banding ligation (EVBL) in the primary prophylaxis of esophageal variceal bleeding. **Material and methods.** Randomized controlled trials were identified through electronic databases, article reference lists and conference proceedings. Analysis was performed using both fixed-effect and random-effect models. Heterogeneity and publication bias were systematically taken into account. Main outcomes were variceal bleeding rates and all-cause mortality, calculated overall and at 6, 12, 18 and 24 months. **Results.** 19 randomized controlled trials were analyzed including a total of 1,483 patients. Overall bleeding rates were significantly lower for the EVBL group: odds ratio (OR) 2.06, 95% confidence interval (CI) [1.55-2.73], $p < 0.0001$, without evidence of publication bias. Bleeding rates were also significantly lower at 18 months (OR 2.20, 95% CI [1.04-4.60], $P = 0.04$), but publication bias was detected. When only high quality trials were taken into account, results for bleeding rates were no longer significant. No significant difference was found for either bleeding-related mortality or for all-cause mortality overall or at 6, 12, 18 or 24 months. BB were associated with more frequent severe adverse events (OR 2.61, 95% CI 1.60-4.40, $P < 0.0001$) whereas fatal adverse events were more frequent with EVBL (OR 0.14, 95% CI 0.02-0.99, $P = 0.05$). **Conclusion.** EVBL appears to be superior to BB in preventing the first variceal bleed, although this finding may be biased as it was not confirmed by high quality trials. No difference was found for mortality. Current evidence is insufficient to recommend EVBL over BB as first-line therapy.

Key words. Variceal bleeding. Banding ligation. β-blockers. Portal hypertension. Cirrhosis.

Neurology®

Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults : Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

S.D. Silberstein, S. Holland, F. Freitag, et al.

Neurology 2012;78:1337
DOI: 10.1212/WNL.0b013e3182535d20

Table 1 Classification of migraine preventive therapies (available in the United States)

Level A: Medications with established efficacy (≥2 Class I trials)	Level B: Medications are probably effective (1 Class I or 2 Class II studies)	Level C: Medications are possibly effective (1 Class II study)	Level U: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as possibly or probably ineffective
Antiepileptic drugs	Antidepressants/ SSRI/SSNRI/TCA	ACE inhibitors	Carbonic anhydrase inhibitor	Established as not effective
Divalproex sodium	Amitriptyline	Lisinopril	Acetazolamide	Antiepileptic drugs
Sodium valproate	Venlafaxine	Angiotensin receptor blockers	Antithrombotics	Lamotrigine
Topiramate	β-Blockers	Candesartan	Acenocoumarol	Probably not effective
β-Blockers	Atenolol[a]	α-Agonists	Coumadin	Clomipramine[a]
Metoprolol	Nadolol[a]	Clonidine[a]	Picotamide	Possibly not effective
Propranolol	Triptans (MRM[b])	Guanfacine[a]	Antidepressants SSRI/SSNRI	Acebutolol[a]
Timolol[a]	Naratriptan[b]	Antiepileptic drugs	Fluvoxamine[a]	Clonazepam[a]
Triptans (MRM[b])	Zolmitriptan[b]	Carbamazepine[a]	Fluoxetine	Nabumetone[a]
Frovatriptan[b]		β-Blockers	Antiepileptic drugs	Oxcarbazepine
		Nebivolol	Gabapentin	Telmisartan
		Pindolol[a]	TCAs	
		Antihistamines	Protriptyline[a]	
		Cyproheptadine	β-Blockers	
			Bisoprolol[a]	

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UTILITY OF ESMOLOL IN THYROID CRISIS

Jasleen Duggal[1], Sarabjeet Singh[1], Paulina Kuchinic[2], Paula Butler[1], Rohit Arora[1]

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ABSTRACT

Thyroid storm is an uncommon but potentially life-threatening manifestation of hyperthyroidism. Mortality can be 30-60% in hospitalized patients unless appropriately treated by combined therapy. We report a case of a 25-year-old African American woman with past medical history of Graves disease and moderately persistent asthma who presented to the emergency department with signs and symptoms of thyrotoxic crisis. Therapy instituted and included the use of an esmolol infusion for control of hypersympathetic activity. A review of the clinical presentation, diagnosis, and management of thyrotoxic crisis is presented along with a discussion on the choice of beta blockade therapy.

Key Words: *Thyroid storm, thyroid crisis, esmolol, beta blockers*

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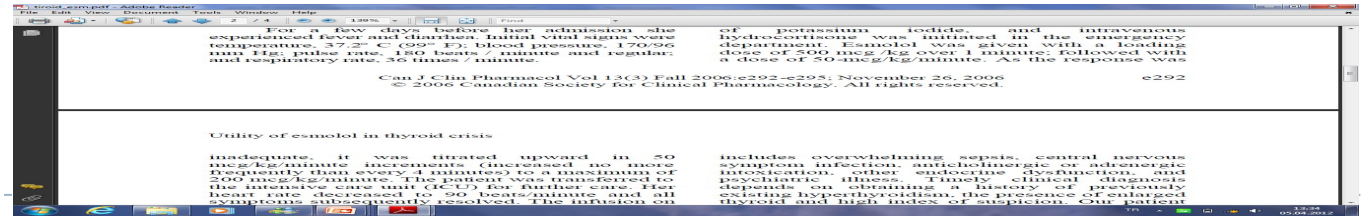

β-Blockade: Benefits Beyond Blood Pressure Reduction?

John R. Cockcroft, MD;[1] Michala E. Pedersen, DPhil[2]

TABLE. Effects of Some Hypertension-Associated Diseases and the Related Effects of Nebivolol

	Hypertension-Associated Diseases			Antihypertensive Treatment
Effect	COPD	Osteoporosis	PAD	Nebivolol
Clinical				
CV risk	↑[20]	↑[81]	↑[5]	↓[a]
Arterial stiffness	↑[27]	↑[83]	↑[118]	↓[14, 66]
Blood pressure	↑[20]	↑[80]	↑[5]	↓[62]
Heart failure	↑[130]	↑[132]	↑[133]	Benefits in seniors[134]
Bone fractures	↑[97]	↑[78]	↑[127]	Benefits plausible[108–110]
Biological				
SNS activity	↑[135]	↑[102, 103]	N/A	↓[62]
Systemic inflammation	↑[28]	↑[87]	↑[121]	↓[63]
Endothelial dysfunction	↑[54]	↑[98]	↑[120]	Improvements observed in vitro[104] and in vivo[65]
Oxidative stress	↑[136]	↑[137]	↑[122]	↓[64]

[a]Data available for elderly patients with heart failure only (SENIORS trial).[134] The symbol "↑" indicates positive correlation, greater risk, or increase; "↓" indicates negative correlation, lower risk, or reduction. Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; N/A, evidence is limited or not available; PAD, peripheral arterial disease; SNS, sympathetic nervous system.

β-Blockade: Benefits Beyond Blood Pressure Reduction?

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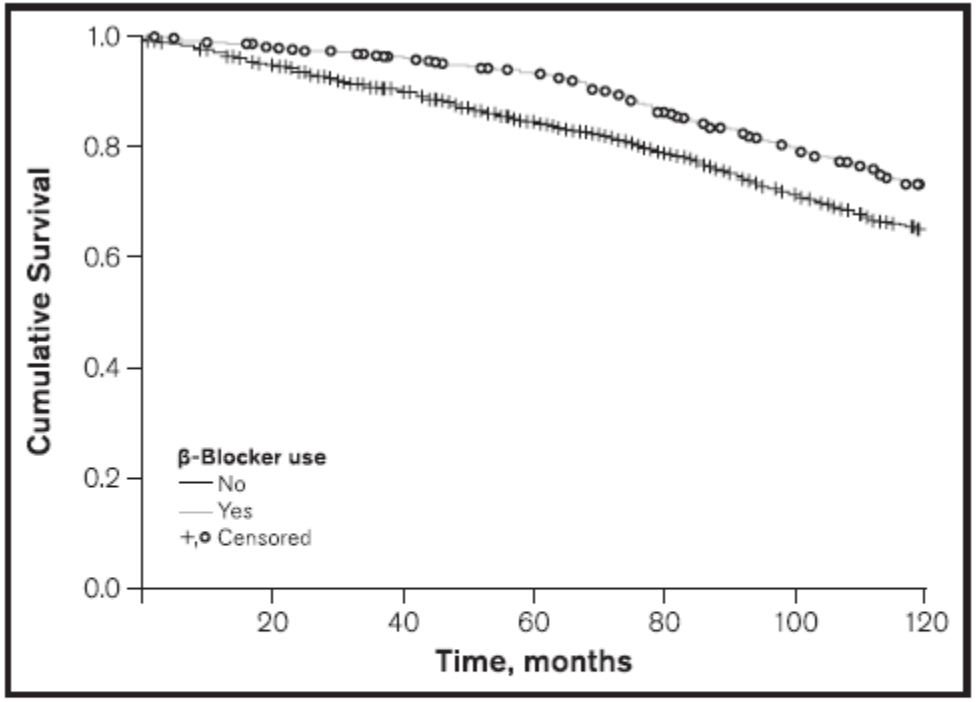

FIGURE 1. The use of β-blockers in patients with chronic obstructive pulmonary disease (COPD) is associated with a higher survival rate than non-use. The symbols "+" and "o" denote time points at which individuals who were ("o") and were not ("+") taking β-blockers either died or dropped out of the study (ie, were "censored"). Adapted with permission from Rutten and colleagues.[74]

β-Blockade: Benefits Beyond Blood Pressure Reduction?

John R. Cockcroft, MD;[1] Michala E. Pedersen, DPhil[2]

·Nebivololün kardiyoselektif, vazodilatötör, antienflamatuvar ve endotel yenileyici özelliklerine sahip olması bu ajanın sadece hipertansiyon tedavisinde değil, KOAH veya osteoporoz gibi durumlarında tedavisinde etkili olmasını sağlıyor.

·Periferik arter hastalığı ile ilgili pek az çalışma olmasına rağmen olumlu etkilerinden bahsedilmektedir.

The Journal of Clinical Hypertension Vol 14 | No 2 | February 2012

Beta-blocker use and COPD mortality: a systematic review and meta-analysis

BMC Pulmonary Medicine 2012, **12**:48 doi:10.1186/1471-2466-12-48

Table 1 Characteristics of included studies in the systematic review

Study	Design	Sample size and cohort description	Type of BB	Relative Risk*	Covariates
Short (2011) [8]	Retrospective Cohort	5,977 COPD patients in Scotland	Cardio-selective	0.78 (0.67-0.92)	CAD and Respiratory disease, age, sex, diabetes, smoking, FEV1, cardiovascular drugs
Au (2004) [6]	Retrospective Cohort	1966-Veteran Affairs Cohort with COPD	Not specified	0.57 (0.33-0.89)	Comorbidity, age, history of COPD, bronchodilators, smoking, coronary artery disease, diabetes
Dransfield (2008) [5]	Retrospective Cohort	825 subjects admitted to hospital for COPD	Not specified	0.39 (0.14-0.99)	Age, CHD, CHF, Liver disease, COPD exacerbations, malignancy, smoking, FEV
Rutten (2007) [9]	Retrospective Cohort	Electronic records of 2,230 patients with COPD in the Netherlands	Selective and non-selective	0.68 (95% - 0.56-0.83), for all BBs: 0.67 (0.55-0.83) for B1 selective BBs. 0.82 (0.61-1.10) for non-selective BBs	Age, sex, diabetes, hypertension, CAD, CVD drugs, pulmonary drugs

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Gottlieb (1998) [11]	Retrospective Cohort	41,814 COPD subjects with previous history of myocardial infarction	Not specified	0.60 (0.57-0.63)	Not specified
Staszewsky (2007) [12]	Retrospective Cohort	628 subjects with class II-IV Heart Failure and COPD	Not specified	0.55 (0.37-0.82)	Not specified
Van Gestel (2008) [13]	Retrospective Cohort	1,205 with vascular disease and COPD in Netherlands	Cardio-selective	0.73 (0.60-0.88)	Age, sex, hypertension, hypercholesterolemia, diabetes, renal function, smoking, BMI, CAD, FEV1, cardiovascular drugs
Chen (2001) [14]	Retrospective Cohort	43,974 subjects with previous history of myocardial infarction and COPD or Asthma	Not specified	0.86 (0.73-1.0)	Age, gender, co-morbidities, CAD, cardiovascular drugs, physician speciality
Hawkins (2009) [15]	Retrospective Cohort	1,258 patients with COPD and previous history of MI	Not specified	0.74 (0.68-0.80)	Not specified

* = Relative risk and 95% confidence interval for beta-blocker use and mortality in COPD

Beta-blocker use and COPD mortality: a systematic review and meta-analysis

BMC Pulmonary Medicine 2012, **12**:48 doi:10.1186/1471-2466-12-48

- Bu çalışma beta blokörlerin KOAH hastalarında mortalite üzerine olumlu katkısı olduğu hipotezini çok kuvvetli şekilde desteklemektedir.
- Altta yatan KOAH hastalığı olup başka sebeplerden dolayı Beta blokör kullanan hastalar beta blokörlerin mortaliteyi düşürücü etkisinden faydalanıyor olmasına rağmen yine de KOAH hastalarında sadece mortaliteyi düşürmek için beta blokör başlamak için daha geniş kontrollü çalışmalara gerek duyulmaktadır.
- KOAH hastalarında gerekli ise beta blokör başlamaktan korkmamalıdır.

Will β-Blockers Live up to the Maxim of Sir James Black, Their Creator?

Khalid Al-Waili, MD[1], Khalid Al-Rasadi, MD[1], and Yajnavalka Banerjee, PhD[1]

"Yeni bir ilaç tedavisi keşfetmenin en iyi yolu, araştırmaya eski bir ilaç ile başlamaktan geçer"

·Powe ve arkadaşlarının küçük bir meme kanseri hastası grubunda yaptığı çalışma beta blokörlerin metastazı kısıtladığını, kanser rekürensini önlediğini ve kansere bağlı mortaliteyi azalttığını göstermiştir.

·Son yıllarda yapılan çalışmalarda ACE inhibitörleri ve anjiotensin 2 reseptör blokörlerinin kanser riskini arttırdığı gösterilmiştir. Ancak Beta blokörlerin bu tip bir etkilerinin olmadığı görülmüştür.

Angiology
63(6) 409-411
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