Journal Club
院外CPAに対する抗不整脈薬

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本日の論文

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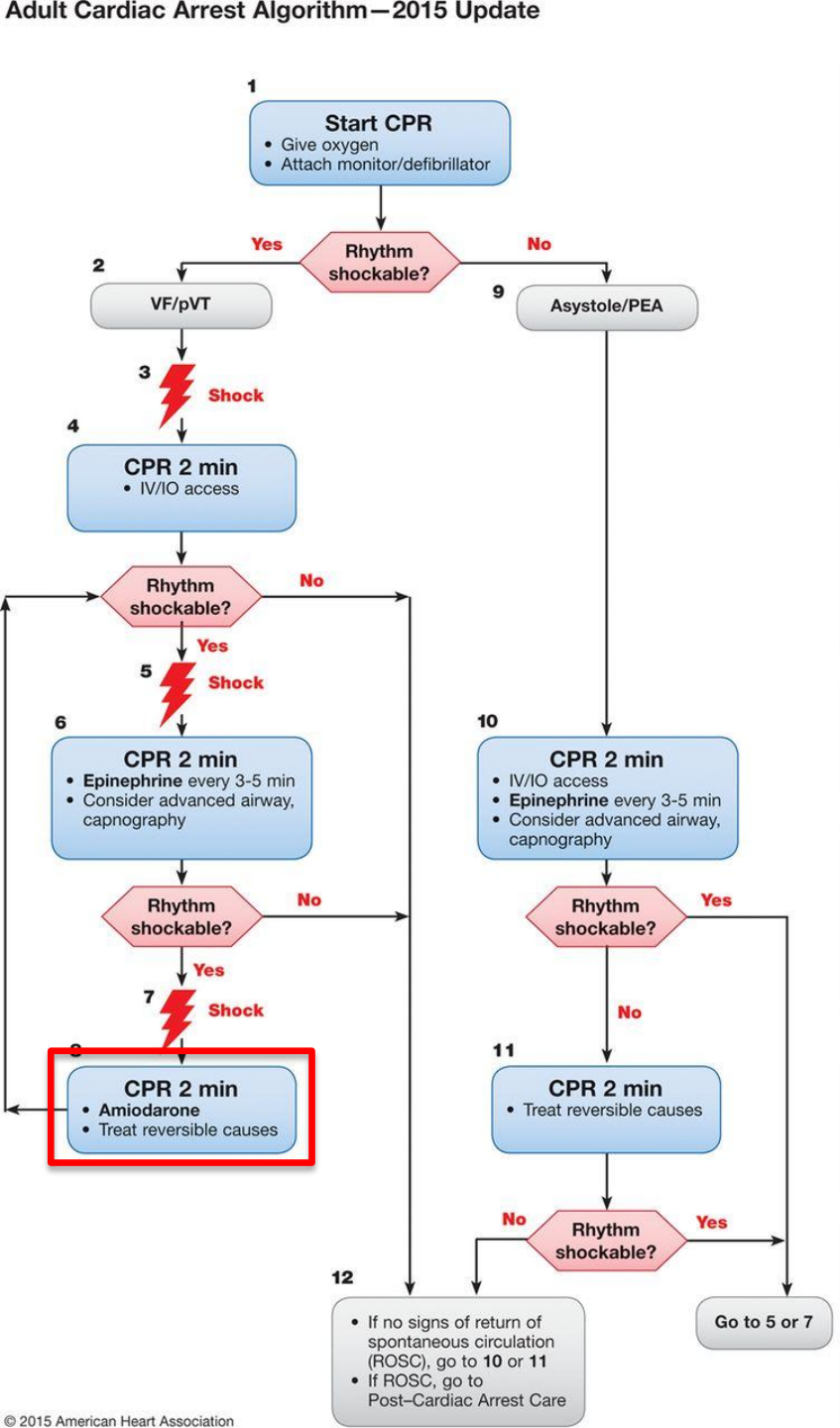
Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest

P.J. Kudenchuk, S.P. Brown, M. Daya, T. Rea, G. Nichol, L.J. Morrison, B. Leroux, C. Vaillancourt, L. Wittwer, C.W. Callaway, J. Christenson, D. Egan, J.P. Ornato, M.L. Weisfeldt, I.G. Stiell, A.H. Idris, T.P. Aufderheide, J.V. Dunford, M.R. Colella, G.M. Vilke, A.M. Brienza, P. Desvigne-Nickens, P.C. Gray, R. Gray, N. Seals, R. Straight, and P. Dorian, for the Resuscitation Outcomes Consortium Investigators*



CPR Quality

- Push hard (at least 2 inches [5 cm]) and fast (100-120/min) and allow complete chest recoil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Rotate compressor every 2 minutes, or sooner if fatigued.
- If no advanced airway, 30:2 compression-ventilation ratio.
- Quantitative waveform capnography
  - If P_{ETCO_2} <10 mm Hg, attempt to improve CPR quality.
- Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality.

Shock Energy for Defibrillation

- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug Therapy

- **Epinephrine IV/IO dose:** 1 mg every 3-5 minutes
- **Amiodarone IV/IO dose:** First dose: 300 mg bolus. Second dose: 150 mg.

Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Abrupt sustained increase in P_{ETCO_2} (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes

- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Drug Therapy

- **Epinephrine IV/IO dose:** 1 mg every 3-5 minutes
- **Amiodarone IV/IO dose:** First dose: 300 mg bolus. Second dose: 150 mg.

AHA2015

ショック抵抗性のVF/pVTに対するアミオダロン投与が推奨されている

アミオダロン

・1960年代に登場した抗不整脈薬で、Vaughan Williams分類でⅢ群に分類される

・急性作用と慢性作用があり、急性作用はNa、Ca、K チャネル、慢性作用はKチャネル、および交感神経α受容体、β受容体が主な標的分子であり、幅広く作用する

薬剤	イオンチャンネル						受容体				ポンプ	臨床効果			心電図所見		
	Na			Ca	K	If	α	β	M_2	A_1	Na-K ATPase	左室機能	洞調律	心外性	PR	QRS	JT
	Fast	Med	Slow														
リドカイン	○											→	→	●			↓
メキシレチン	○											→	→	●			↓
プロカインアミド		Ⓐ			●							↓	→	●	↑	↑	↑
ジソピラミド			Ⓐ		●				○			↓	→	●	↑↓	↑	↑
キニジン		Ⓐ			●		○		○			→	↑	●	↑↓	↑	↑
ブロバフェノン		Ⓐ						●				↓	↓	○	↑	↑	
アプリンジン		Ⓘ		○	○	○						→	→	●	↑	↑	→
シベンゾリン			Ⓐ	○	●				○			↓	→	○	↑	↑	→
ピルメノール			Ⓐ		●				○			↓	↑	○	↑	↑	↑→
フレカイニド			Ⓐ		○							↓	→	○	↑	↑	
ピルジカイニド			Ⓐ									↓	→	○	↑	↑	
ベプリジル	○			●	●							→	↓	○			↑
ベラパミル	○			●			●					↓	↓	○	↑		
ジルチアゼム				●								↓	↓	○	↑		
ソタロール					●			●				↓	↓	○	↑		↑
アミオダロン	○			○	●		●	●				→	↓	●	↑		↑
ニフェカラント					●							→	→	○			↑
ナドロール								●				↓	↓	○	↑		
プロプラノロール	○							●				↓	↓	○	↑		
アトロピン									●			→	↑	●	↓		
ATP										■		?	↓	○	↑		
ジゴキシン									■		●	↑	↓	●	↑		↓

遮断作用の相対的強さ：○低　●中等　●高

不整脈薬物治療に関するガイドライン（2009年改訂版）

ARREST

Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation

3回以上の除細動が無効な

VF/pVTによる非外傷性院外CPAを対象に

アミオダロン投与群(246人) vs Placebo群(258人)で

自己心拍再開率と病院到着時の生存率を比較

N Engl J Med. 1999 Sep 16;341(12):871-8

ARREST

Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation

病院到着時の生存率はアミオダロン投与群で有意に高かった
(p=0.03)

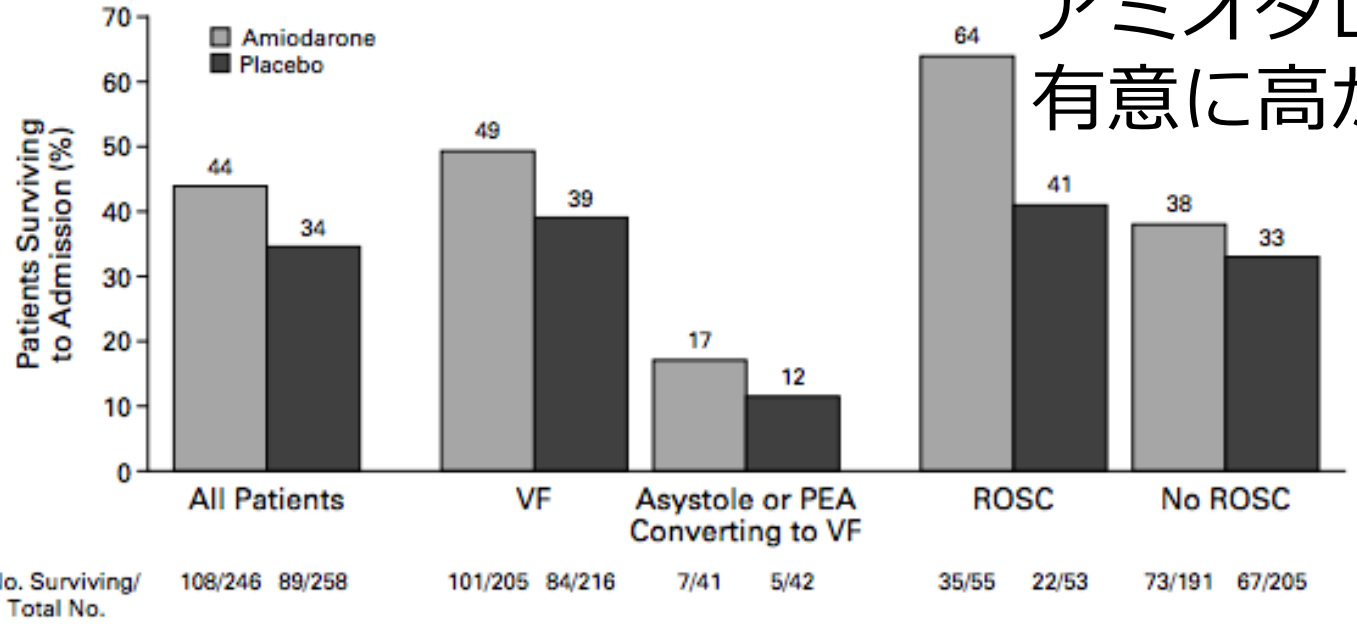


Figure 1. Effect of Treatment with Amiodarone or Placebo on the Rate of Survival to Hospital Admission in All Patients and Subgroups of Patients.

VF denotes ventricular fibrillation, PEA pulseless electrical activity, and ROSC return of spontaneous circulation before administration of the study drug. Values above the bars are the percentages of patients who survived to admission.

N Engl J Med. 1999 Sep 16;341(12):871-8

ALIVE

Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation

院外でVFとなり、3回の除細動が無効で

　　アドレナリン投与+4回目の除細動も無効な例

または 除細動が成功したが再発した例を対象に

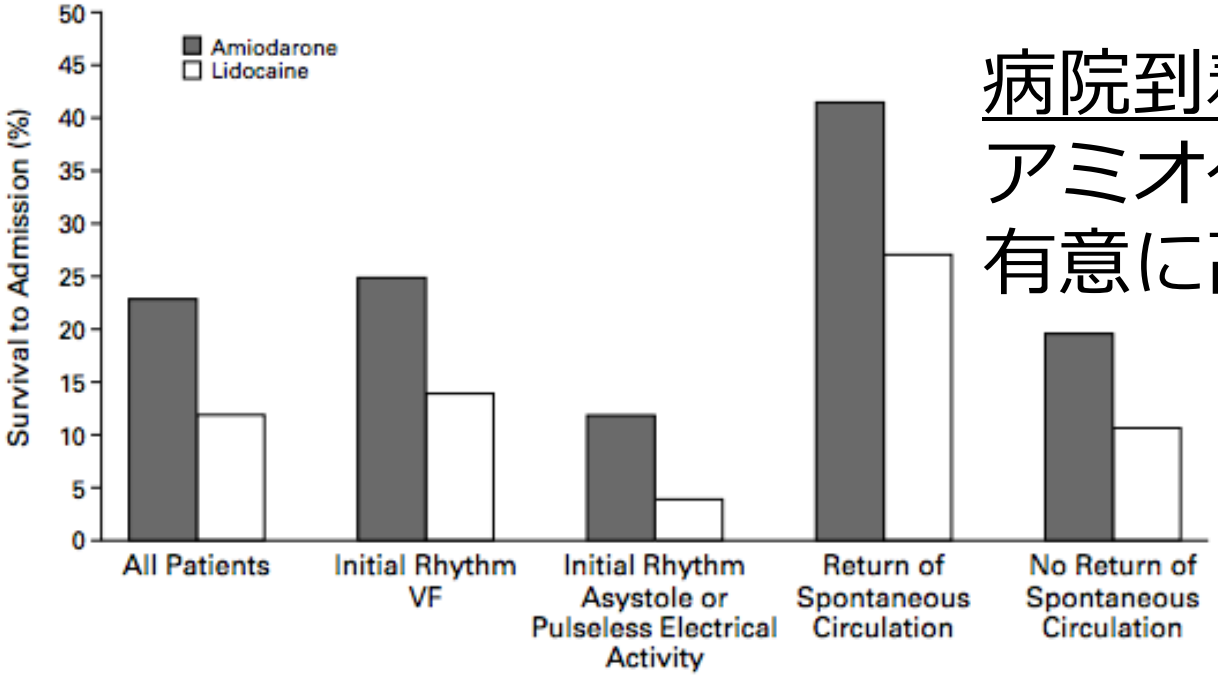
アミオダロン群(180人) vs リドカイン群(167人)で

病院到着時の生存率を比較

N Engl J Med. 2002 Mar 21;346(12):884-90

ALIVE

Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation



No. Surviving/Total No.					
Amiodarone	41/80	35/141	4/34	10/24	31/156
Lidocaine	20/167	19/134	1/27	3/11	17/156

Figure 1. Effect of Treatment with Amiodarone or Lidocaine on the Rate of Survival to Hospital Admission in All Patients and in Selected Subgroups.

VF denotes ventricular fibrillation. Return of spontaneous circulation refers to transient return before the administration of the study drug.

<u>病院到着時の生存率</u>はアミオダロン投与群で有意に高かった
(p=0.009)

N Engl J Med. 2002 Mar 21;346(12):884-90

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背景

アミオダロンとリドカインは一般的に除細動の成功と再発の防止のために使用される

過去の研究で院外CPAに対してアミオダロンはPlacebo、リドカインと比較して、自己心拍再開や病院到着時の生存率が優れている傾向が示されたが、アミオダロンの長期生存率や神経学的予後に対する効果は不確かである

院外CPAにおいてアミオダロン、リドカイン、Placeboでの退院時生存率を比較検討する

論文のPICO

P：非外傷性院外CPAで
ショック抵抗性のVF/pVT患者が

I：アミオダロンの投与を受けることは

C：投与を受けない場合(リドカイン/Placebo)と比較し

O：退院時生存率が改善するか

方法

- 多施設二重盲検化比較試験
- 2012.5.7 - 2015.10.25
- USA、カナダの55のEMSが参加
- 同意取得はされていない
- NHLBI、the Canadian Institutes of Health Researchなどから資金提供を受けた。またBaxter Healthcare社より試薬を無償での提供を受けたが、研究計画への参加はしていない
- Per-protocol解析

対象患者

Inclusion

- 18歳以上
- 非外傷性の院外CPA
- 蘇生中に少なくとも1回除細動を受けたもの
- 静脈路、骨髄路を確保されたもの

Exclusion

- Open labelの抗不整脈薬を投与されたもの
- アミオダロン、リドカインへの過剰反応あり
- 妊婦、囚人、小児
- 研究への不参加を表明したもの

介入

- 試薬はそれぞれ中身が分からないようシリンジに入れてある
- シリンジは3本セットで1つのキットとなる
- それぞれのEMSに1:1:1の割合でランダムにキットを配布する

Study Drug Kit Contents (Treatment Assignment)

Amiodarone (PM101) Arm	Lidocaine Arm	Placebo Arm
PM101 150 mg (3cc)	Lidocaine 60 mg (3 cc)	Placebo (3cc)
PM101 150 mg (3cc)	Lidocaine 60 mg (3cc)	Placebo (3cc)
PM101 150 mg (3cc)	Lidocaine 60 mg (3cc)	Placebo (3cc)

プロトコール

- 各EMSによりAHAガイドラインに沿って蘇生を開始する
- 1回以上の除細動で失敗または再発を認め、研究の条件を満たした場合、キットを開封し試薬を投与する
- 初回投与は2シリンジ分投与し、次の投与サイクルには残り1シリンジを投与する
(ただし体重が45.4kg以下であれば初回投与は1シリンジ分とした)

プロトコール

- 病院到着後は引き続きAHAガイドラインに沿って加療を継続する
- この際には必要であればopen-labelのアミオダロンまたはリドカインを使用することができる
- もし病院到着前に使用した試薬の情報が緊急に必要な場合には治療する医師のみに情報を伝える

Primary Outcome

退院時生存率

- 今研究の主な目的は
  - ・アミオダロン vs Placebo

  次に
  - ・リドカイン vs Placebo
  - ・アミオダロン vs リドカイン

    それぞれの退院時生存率を比較することである

Secondary Outcome

神経学的予後

- Modified Rankin scale3点以下かどうか

Modified Rankin scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

＊Primary/SecondaryともにPer-Protocolで解析

＊ITTでも解析はしている

その他のOutcome

- 入院後に受けた除細動の回数
- 病院到着時までの自己心拍再開率
- 病院到着後の治療内容
- 蘇生中止までの時間

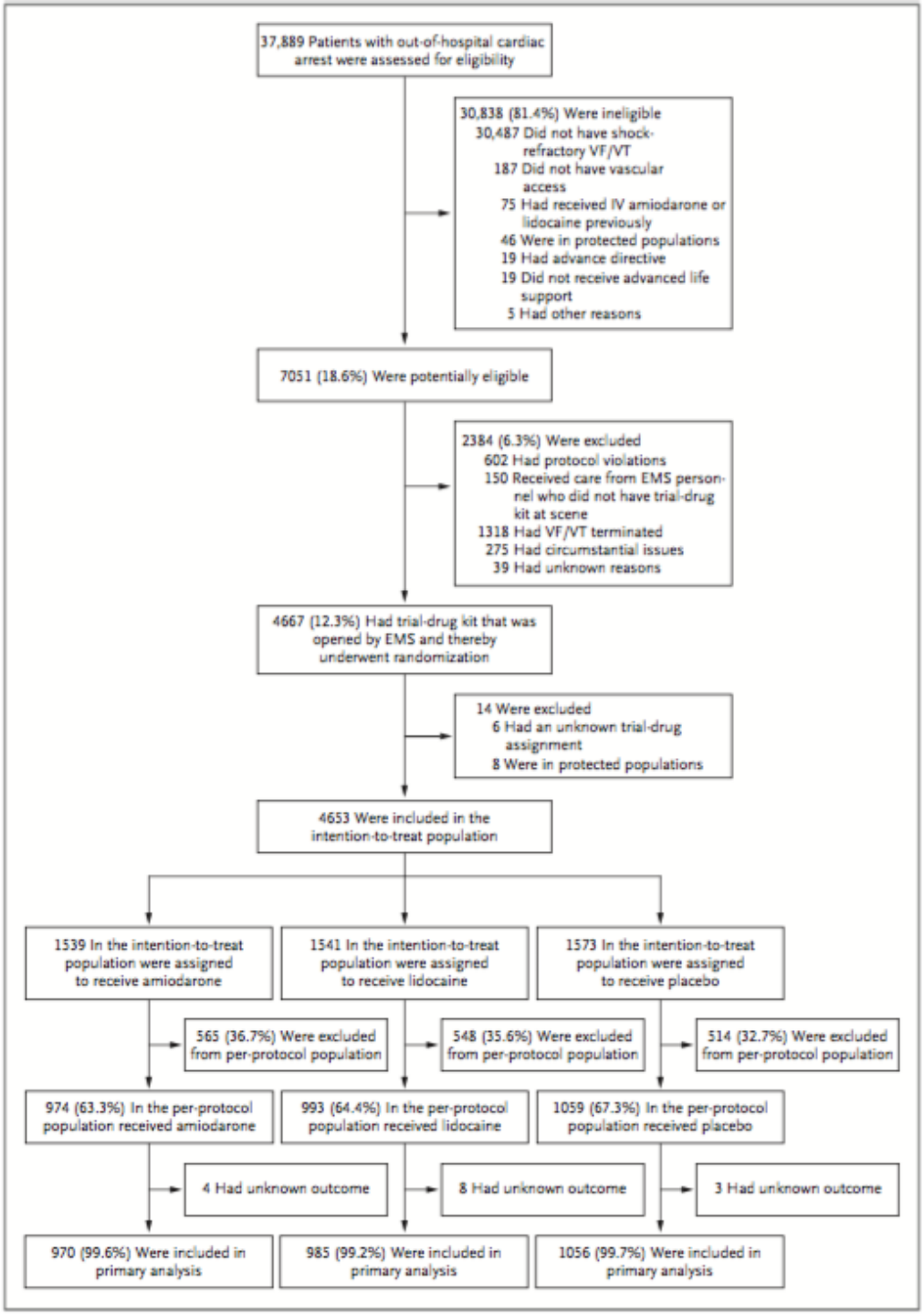
Subgroup解析

- 目撃者の有無(bystander, EMS, or not)
- Bystander CPRの有無
- CPAとなった場所(Public or Private)
- 試薬使用までの時間(<15min or not)
- 試薬投与経路(経静脈路 or 経骨髄路)
- 他の試験に参加していたか(CCC vs ICC)
- 各地域における元々のCPR生存率
- 薬剤投与protocol

統計解析

- 検出力90%、有意水準0.05で
- 退院時生存率6.3%(29.7%⇒23.4%)の差を出すため、サンプルサイズを対象患者3000人(各群1000人)と設定した
- P値は0.05以下で有意
- Per-protocol解析を使用

  ＊ただしITTでも解析はしている



結果

期間内に37889人の非外傷性院外CPA

↓

7051人(18.6%)がpotentially eligible

↓

2384人がexcluded
- 1318人 VF/VT terminated
- 602人 protocol violations
- 275人 circumstantial issues
- 150人 did not have kit
- 39人 unknown reason

↓

4667人が試薬使用

↓

14人がexcluded
- 6人 unknown trial-drug
- 8人 protected population

↓

4653人がInclusion

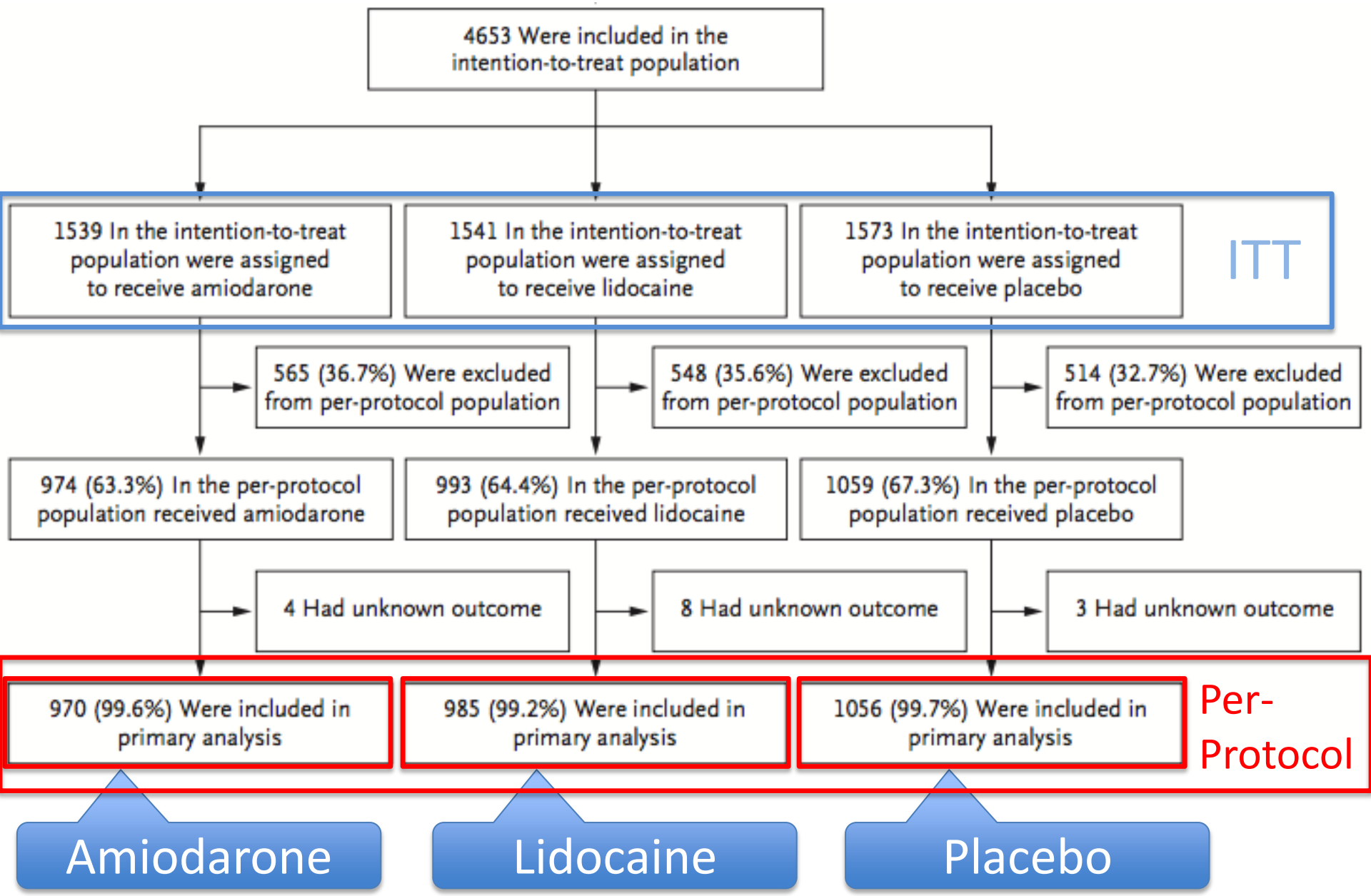

4653 Were included in the intention-to-treat population
1539 In the intention-to-treat population were assigned to receive amiodarone
1541 In the intention-to-treat population were assigned to receive lidocaine
1573 In the intention-to-treat population were assigned to receive placebo
ITT
565 (36.7%) Were excluded from per-protocol population
548 (35.6%) Were excluded from per-protocol population
514 (32.7%) Were excluded from per-protocol population
974 (63.3%) In the per-protocol population received amiodarone
993 (64.4%) In the per-protocol population received lidocaine
1059 (67.3%) In the per-protocol population received placebo
4 Had unknown outcome
8 Had unknown outcome
3 Had unknown outcome
970 (99.6%) Were included in primary analysis
985 (99.2%) Were included in primary analysis
1056 (99.7%) Were included in primary analysis
Per-Protocol
Amiodarone
Lidocaine
Placebo

Table S1. Numbers of Patients from the Intention-to-Treat Population That Were Excluded from the Per-Protocol Population by Treatment Arm

	Amiodarone (N = 1539)	Lidocaine (N = 1541)	Placebo (N = 1573)	Total (N = 4653)
Patients who did not meet eligibility criteria				
No shock refractory VF/VT, n (%)	82 (5.3%)	85 (5.5%)	103 (6.5%)	270 (5.8%)
Advance directive, n (%)	8 (0.5%)	7 (0.5%)	3 (0.2%)	18 (0.4%)
Prior IV administration of amiodarone or lidocaine, n (%)	5 (0.3%)	4 (0.3%)	2 (0.1%)	11 (0.2%)
No vascular access, n (%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	4 (0.1%)
Exsanguination, n (%)	2 (0.1%)	1 (0.1%)	0 (0%)	3 (0.1%)
History of allergy to amiodarone or lidocaine, n (%)	0 (0%)	0 (0%)	1 (0.1%)	1 (0.0%)
Total number of patients who did not meet eligibility criteria, n (%)	98 (6.4%)	99 (6.4%)	110 (7.0%)	307 (6.6%)
Study drug not given, n (%)	79 (5.1%)	91 (5.9%)	88 (5.6%)	257 (5.5%)
Non-shockable initial rhythm, n (%)	389 (25.3%)	358 (23.2%)	316 (20.1%)	1063 (22.8%)
Total number of patients excluded, n (%)	565 (36.7%)	548 (35.6%)	514 (32.7%)	1627 (35.0%)

Exclusionされた理由は各群に大きな違いはない

Table 1. Prerandomization Characteristics of the Per-Protocol Population.*

Characteristic	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)
Age — yr	63.7±14.0	63.0±14.7	62.7±14.6
Male sex — no./total no. (%)	762/973 (78.3)	816/993 (82.2)	844/1059 (79.7)
Cardiac arrest occurred in public location — no./total no. (%)	303/974 (31.1)	312/993 (31.4)	316/1056 (29.9)
Cardiac arrest witnessed — no./total no. (%)			
By EMS	57/950 (6.0)	44/965 (4.6)	54/1027 (5.3)
By bystander	621/950 (65.4)	636/965 (65.9)	687/1027 (66.9)
Bystander-initiated PAD shock — no./total no. (%)	62/905 (6.9)	51/927 (5.5)	57/988 (5.8)
Bystander-initiated CPR — no./total no. (%)	556/905 (61.4)	549/927 (59.2)	595/988 (60.2)
Time from initial call†			
To first arrival of EMS — min	5.8±2.6	5.6±2.4	5.8±2.6
To first arrival of EMS ≤4 min — no./total no. (%)	209/973 (21.5)	237/992 (23.9)	244/1058 (23.1)
To first arrival of ALS — min	8.0±5.1	7.8±4.3	8.0±4.6
Trial site — no. (%)			
A	104 (10.7)	97 (9.8)	92 (8.7)
B	154 (15.8)	158 (15.9)	162 (15.3)
C	74 (7.6)	77 (7.8)	80 (7.6)
D	59 (6.1)	60 (6.0)	66 (6.2)
E	4 (0.4)	8 (0.8)	7 (0.7)
F	215 (22.1)	223 (22.5)	260 (24.6)
G	21 (2.2)	14 (1.4)	15 (1.4)
H	163 (16.7)	149 (15.0)	169 (16.0)
I	63 (6.5)	85 (8.6)	80 (7.6)
J	117 (12.0)	122 (12.3)	128 (12

* Plus–minus values are means ±SD. No baseline factors varied significantly according to trial group (P>0.05). ALS denotes advanced life support, CPR cardiopulmonary resuscitation, EMS emergency medical services, and PAD public-access defibrillation.

† Initial call refers to the initial notification of an occurrence of cardiac arrest to an emergency call center.

各群のbaselineに明らかな差はない

Table 2. Event Characteristics and Treatments Received in the Per-Protocol Population.*

Characteristic	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)	Overall P Value
Time from initial call to first dose of trial drug in patients with non–EMS-witnessed cardiac arrest — min	19.3±7.1	19.3±7.6	19.3±7.3	0.81
Time from cardiac arrest to first dose of trial drug in patients with EMS-witnessed arrest — min	11.7±5.8	12.1±6.6	12.1±6.6	0.91
Time from initial call to first dose of epinephrine — min	16.1±6.5	15.8±6.1	16.2±6.4	0.35
Trial drug given through intraosseous access — no./total no. (%)†	212/974 (21.8)	220/991 (22.2)	229/1054 (21.7)	0.96
Syringes of trial drug given — no./total no. (%)				<0.001
3 syringes	621/967 (64.2)	594/981 (60.6)	758/1051 (72.1)	
2 syringes	327/967 (33.8)	368/981 (37.5)	273/1051 (26.0)	
1 syringe	19/967 (2.0)	19/981 (1.9)	20/1051 (1.9)	
Prehospital advanced airway management successful — no. (%)	819 (84.1)	854 (86.0)	893 (84.3)	0.45
CPR-process measures in first 10 min after pad placement				
Pre-shock pause — sec‡	10.2±10.7	10.2±9.0	10.2±9.0	0.99
Post-shock pause — sec‡	5.1±6.7	5.2±10.6	5.8±10.0	0.19
Compression rate/min	110.3±10.7	110.7±10.5	110.7±10.9	0.63
Compression depth — mm	50.9±9.2	51.5±10.5	52.0±9.8	0.22
CPR fraction§	0.83±0.09	0.84±0.09	0.83±0.10	0.58
No. of EMS shocks — median (IQR)	5 (3–7)	5 (3–7)	6 (4–9)	<0.001
No. of shocks before first dose of trial drug — median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.73
No. of EMS shocks after first dose of trial drug — median (IQR)	2 (1–4)	2 (1–3)	3 (1–6)	<0.001
Prehospital drugs administered				
Epinephrine — no. (%)	961 (98.7)	981 (98.8)	1046 (98.8)	1.00
Vasopressin — no./total no. (%)	67/974 (6.9)	60/992 (6.0)	55/1059 (5.2)	0.28
Bicarbonate — no. (%)	271 (27.8)	258 (26.0)	308 (29.1)	0.29
Atropine — no./total no. (%)	52/974 (5.3)	43/992 (4.3)	33/1059 (3.1)	0.04
Beta-blocker — no./total no. (%)	6/974 (0.6)	2/992 (0.2)	10/1059 (0.9)	0.09
Open-label lidocaine — no./total no. (%)	4/974 (0.4)	6/992 (0.6)	13/1059 (1.2)	0.08
Open-label amiodarone — no./total no. (%)	7/974 (0.7)	13/992 (1.3)	15/1059 (1.4)	0.29
Procainamide — no./total no. (%)	67/974 (6.9)	57/992 (5.7)	92/1059 (8.7)	0.03
Magnesium — no./total no. (%)	78/974 (8.0)	68/992 (6.8)	119/1059 (11.2)	0.001
Coenrollment in CPR trial — no./total no. (%)¶				0.95
Received continuous chest compressions	234/973 (24.0)	249/993 (25.1)	253/1059 (23.9)	
Received interrupted chest compressions	264/973 (27.1)	259/993 (26.1)	290/1059 (27.4)	
Were not enrolled in CPR trial	475/973 (48.8)	485/993 (48.8)	516/1059 (48.7)	

Table 3. Outcomes According to Trial Group in the Per-Protocol Population.*

Outcome	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)	Amiodarone vs. Placebo		Lidocaine vs. Placebo		Amiodarone vs. Lidocaine	
				Difference (95% CI) *percentage points*	P Value	Difference (95% CI) *percentage points*	P Value	Difference (95% CI) *percentage points*	P Value
Primary outcome: survival to discharge — no./total no. (%)†	237/970 (24.4)	233/985 (23.7)	222/1056 (21.0)	3.2 (−0.4 to 7.0)	0.08	2.6 (−1.0 to 6.3)	0.16	0.7 (−3.2 to 4.7)	0.70
Secondary outcome: modified Rankin score ≤3 — no./total no. (%)‡	182/967 (18.8)	172/984 (17.5)	175/1055 (16.6)	2.2 (−1.1 to 5.6)	0.19	0.9 (−2.4 to 4.2)	0.59	1.3 (−2.1 to 4.8)	0.44
Mechanistic (exploratory) outcomes									
Return of spontaneous circulation at ED arrival — no./total no. (%)	350/974 (35.9)	396/992 (39.9)	366/1059 (34.6)	1.4 (−2.8 to 5.5)	0.52	5.4 (1.2 to 9.5)	0.01	−4.0 (−8.3 to 0.3)	0.07
Admitted to hospital — no. (%)	445 (45.7)	467 (47.0)	420 (39.7)	6.0 (1.7 to 10.3)	0.01	7.4 (3.1 to 11.6)	<0.001	−1.3 (−5.7 to 3.1)	0.55
Modified Rankin score in all patients‡	5.0±1.9	5.1±1.8	5.2±1.8	−0.14 (−0.30 to 0.02)	0.09	−0.06 (−0.22 to 0.10)	0.45	−0.08 (−0.24 to 0.08)	0.34
Modified Rankin score in survivors‡	2.0±2.7	2.2±2.7	2.0±2.6						
Distribution of modified Rankin scores — no./total no. (%)‡									
0	60/966 (6.2)	49/981 (5.0)	55/1053 (5.2)						
1	47/966 (4.9)	37/981 (3.8)	39/1053 (3.7)						
2	41/966 (4.2)	46/981 (4.7)	40/1053 (3.8)						
3	34/966 (3.5)	37/981 (3.8)	41/1053 (3.9)						
4	31/966 (3.2)	36/981 (3.7)	27/1053 (2.6)						
5	21/966 (2.2)	24/981 (2.4)	18/1053 (1.7)						
6	732/966 (75.8)	752/981 (76.7)	833/1053 (79.1)						

Primary/Secondaryともに各群間での差はなし

Primary： 24.4% vs 23.7% vs 21.0%

Secondary： 18.8% vs 17.5% vs 16.6%

Table S2. Survival to Discharge in A Priori Subgroups in the Per-Protocol Population

	Amiodarone	Lidocaine	Placebo	Amiodarone vs Placebo Difference (95% CI) P	Lidocaine vs Placebo Difference (95% CI) P	Amiodarone vs Lidocaine Difference (95% CI) P	P for Interaction
Witnessed status							0.05
EMS witnessed, n (%) [N=57;43;54]	22 (38.6%)	10 (23.3%)	9 (16.7%)	21.9% (5.8%, 38.0%) P=0.01	6.6% (-9.5%, 22.7%) P=0.42	15.3% (-2.6%, 33.2%) P=0.09	
Bystander witnessed, n (%) [N=618;632;684]	171 (27.7%)	176 (27.8%)	155 (22.7%)	5.0% (0.3%, 9.7%) P=0.04	5.2% (0.5%, 9.9%) P=0.03	-0.1% (-5.1%, 4.9%) P=0.97	
Unwitnessed, n (%) [N=271;282;286]	41 (15.1%)	45 (16.0%)	48 (16.8%)	-1.7% (-7.8%, 4.4%) P=0.58	-0.8 (-6.9%, 5.3%) P=0.80	-0.9% (-6.9%, 5.1%) P=0.77	

目撃がある場合、抗不整脈薬群はPlacebo群に比較して
生存率が有意に高いが、目撃がない場合は両群間に差はない

Table 2. Event Characteristics and Treatments Received in the Per-Protocol Population.*

Characteristic	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)	Overall P Value
Time from initial call to first dose of trial drug in patients with non–EMS-witnessed cardiac arrest — min	19.3±7.1	19.3±7.6	19.3±7.3	0.81
Time from cardiac arrest to first dose of trial drug in patients with EMS-witnessed arrest — min	11.7±5.8	12.1±6.6	12.1±6.6	0.91
Time from initial call to first dose of epinephrine — min	16.1±6.5	15.8±6.1	16.2±6.4	0.35
Trial drug given through intraosseous access — no./total no. (%)†	212/974 (21.8)	220/991 (22.2)	229/1054 (21.7)	0.96
Syringes of trial drug given — no./total no. (%)				<0.001
3 syringes	621/967 (64.2)	594/981 (60.6)	758/1051 (72.1)	
2 syringes	327/967 (33.8)	368/981 (37.5)	273/1051 (26.0)	
1 syringe	19/967 (2.0)	19/981 (1.9)	20/1051 (1.9)	
Prehospital advanced airway management successful — no. (%)	819 (84.1)	854 (86.0)	893 (84.3)	0.45
CPR-process measures in first 10 min after pad placement				
Pre-shock pause — sec‡	10.2±10.7	10.2±9.0	10.2±9.0	0.99
Post-shock pause — sec‡	5.1±6.7	5.2±10.6	5.8±10.0	0.19
Compression rate/min	110.3±10.7	110.7±10.5	110.7±10.9	0.63
Compression depth — mm	50.9±9.2	51.5±10.5	52.0±9.8	0.22
CPR fraction§	0.83±0.09	0.84±0.09	0.83±0.10	0.58
No. of EMS shocks — median (IQR)	5 (3–7)	5 (3–7)	6 (4–9)	<0.001
No. of shocks before first dose of trial drug — median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.73
No. of EMS shocks after first dose of trial drug — median (IQR)	2 (1–4)	2 (1–3)	3 (1–6)	<0.001
Prehospital drugs administered				
Epinephrine — no. (%)	961 (98.7)	981 (98.8)	1046 (98.8)	1.00
Vasopressin — no./total no. (%)	67/974 (6.9)	60/992 (6.0)	55/1059 (5.2)	0.28
Bicarbonate — no. (%)	271 (27.8)	258 (26.0)	308 (29.1)	0.29
Atropine — no./total no. (%)	52/974 (5.3)	43/992 (4.3)	33/1059 (3.1)	0.04
Beta-blocker — no./total no. (%)	6/974 (0.6)	2/992 (0.2)	10/1059 (0.9)	0.09
Open-label lidocaine — no./total no. (%)	4/974 (0.4)	6/992 (0.6)	13/1059 (1.2)	0.08
Open-label amiodarone — no./total no. (%)	7/974 (0.7)	13/992 (1.3)	15/1059 (1.4)	0.29
Procainamide — no./total no. (%)	67/974 (6.9)	57/992 (5.7)	92/1059 (8.7)	0.03
Magnesium — no./total no. (%)	78/974 (8.0)	68/992 (6.8)	119/1059 (11.2)	0.001
Coenrollment in CPR trial — no./total no. (%)¶				0.95
Received continuous chest compressions	234/973 (24.0)	249/993 (25.1)	253/1059 (23.9)	
Received interrupted chest compressions	264/973 (27.1)	259/993 (26.1)	290/1059 (27.4)	
Were not enrolled in CPR trial	475/973 (48.8)	485/993 (48.8)	516/1059 (48.7)	

Placebo群では
薬剤投与量が
多い

Shockの回数や
他の薬剤投与数も
多い

Table 3. Outcomes According to Trial Group in the Per-Protocol Population.*

Outcome	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)	Amiodarone vs. Placebo		Lidocaine vs. Placebo		Amiodarone vs. Lidocaine	
				Difference (95% CI) *percentage points*	P Value	Difference (95% CI) *percentage points*	P Value	Difference (95% CI) *percentage points*	P Value
Primary outcome: survival to discharge — no./total no. (%)†	237/970 (24.4)	233/985 (23.7)	222/1056 (21.0)	3.2 (−0.4 to 7.0)	0.08	2.6 (−1.0 to 6.3)	0.16	0.7 (−3.2 to 4.7)	0.70
Secondary outcome: modified Rankin score ≤3 — no./total no. (%)‡	182/967 (18.8)	172/984 (17.5)	175/1055 (16.6)	2.2 (−1.1 to 5.6)	0.19	0.9 (−2.4 to 4.2)	0.59	1.3 (−2.1 to 4.8)	0.44
Mechanistic (exploratory) outcomes									
Return of spontaneous circulation at ED arrival — no./total no. (%)	350/974 (35.9)	396/992 (39.9)	366/1059 (34.6)	1.4 (−2.8 to 5.5)	0.52	5.4 (1.2 to 9.5)	0.01	−4.0 (−8.3 to 0.3)	0.07
Admitted to hospital — no. (%)	445 (45.7)	467 (47.0)	420 (39.7)	6.0 (1.7 to 10.3)	0.01	7.4 (3.1 to 11.6)	<0.001	−1.3 (−5.7 to 3.1)	0.55
Modified Rankin score in all patients‡	5.0±1.9	5.1±1.8	5.2±1.8	−0.14 (−0.30 to 0.02)	0.09	−0.06 (−0.22 to 0.10)	0.45	−0.08 (−0.24 to 0.08)	0.34
Modified Rankin score in survivors‡	2.0±2.7	2.2±2.7	2.0±2.6						
Distribution of modified Rankin scores — no./total no. (%)‡									
0	60/966 (6.2)	49/981 (5.0)	55/1053 (5.2)						
1	47/966 (4.9)	37/981 (3.8)	39/1053 (3.7)						
2	41/966 (4.2)	46/981 (4.7)	40/1053 (3.8)						
3	34/966 (3.5)	37/981 (3.8)	41/1053 (3.9)						
4	31/966 (3.2)	36/981 (3.7)	27/1053 (2.6)						
5	21/966 (2.2)	24/981 (2.4)	18/1053 (1.7)						
6	732/966 (75.8)	752/981 (76.7)	833/1053 (79.1)						

リドカイン投与群でROSC率が高い傾向がある

抗不整脈薬群はPlacebo群に比較して病院到着時の生存率が高い

Table S3. Emergency Department and Hospital Treatments Received in the Per-Protocol Population

	Amiodarone	Lidocaine	Placebo	P-value
Emergency Department/Hospital Procedures (among patients transported to hospital)				
Antiarrhythmic therapy within 24 hours, n (%) [N=801;815;874]	418 (52%)	472 (58%)	492 (56%)	0.05
Amiodarone within 24 hours, n (%) [N=801;814;874]	283 (35%)	372 (46%)	385 (44%)	<0.001
Lidocaine within 24 hours, n (%) [N=801;814;873]	50 (6%)	56 (7%)	66 (8%)	0.57
Any CPR, n (%) [N=803;817;876]	525 (65%)	519 (64%)	610 (70%)	0.03
Hospital Procedures (among patients admitted to hospital)				
Targeted temperature management, n (%) [N=443;466;418]	337 (76%)	349 (75%)	300 (72%)	0.28
Coronary Catheterization in first 24 hours, n (%) [N=444;466;419]	253 (57%)	262 (56%)	232 (55%)	0.87
Implantable cardiovascular defibrillator, n (%) [N=443;462;417]	88 (20%)	81 (18%)	79 (19%)	0.68
Care limited or withdrawn, n (%) [N=445;467;420]	136 (31%)	144 (31%)	114 (27%)	0.40
Care limited or withdrawn within 3 days of arrest, n (%) [N=445;467;420]	51 (11%)	45 (10%)	53 (13%)	0.37
Hospital Procedures (among patients discharged alive)				
Implantable cardiovascular defibrillator, n (%) [N=237;233;114]	88 (37%)	80 (35%)	79 (36%)	0.87

アミオダロン群では24時間以内にopen-labelのアミオダロン使用率が低い

抗不整脈薬群では24時間以内にCPRを施行されない傾向がある

Table 4. Adverse Events in the Per-Protocol Population.*

Event	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)	Overall P Value
	number (percent)			
Thrombophlebitis within 24 hr	1 (0.1)	3 (0.3)	2 (0.2)	0.61
Anaphylaxis within 24 hr	0	0	0	NA
Clinical seizure activity within 24 hr	31 (3.2)	51 (5.1)	39 (3.7)	0.07
Temporary cardiac pacing within 24 hr†	48 (4.9)	32 (3.2)	29 (2.7)	0.02
Complications of intravenous or intraosseous access within 24 hr	2 (0.2)	0	2 (0.2)	0.37
Any nonfatal serious adverse event within 24 hr‡§	11 (1.1)	12 (1.2)	4 (0.4)	0.09
Any nonfatal adverse event within 24 hr§	81 (8.3)	84 (8.5)	69 (6.5)	0.18
Death before hospital discharge	733 (75.3)	752 (75.7)	834 (78.8)	0.16
Any adverse event within 24 hr or death before hospital discharge	763 (78.3)	775 (78.0)	851 (80.4)	0.20

薬剤関連の有害事象に関しては各群間で有意な差はなかったが、
一時ペーシングはアミオダロン群で多い傾向にあった

Table S5. Pre-Randomization Characteristics of the Intention-to-Treat Population[1]

	Amiodarone (N=1539)	Lidocaine (N=1541)	Placebo (N=1573)
Age (y), mean (sd) [N=1538;1541;1573;4658]	64.4 (14.9)	63.6 (15.4)	63.4 (15.1)
Male, n (%) [N=1538;1541;1573;4658]	1173 (76.3%)	1212 (78.7%)	1193 (75.8%)
Public Location, n (%) [N=1536;1541;1570;4653]	404 (26.3%)	409 (26.5%)	408 (26.0%)
Witness Status, n (%) [N=1500;1501;1534;4541]			
EMS Witnessed	103 (6.9%)	105 (7.0%)	108 (7.0%)
Bystander Witnessed	877 (58.5%)	886 (59.0%)	926 (60.4%)
Bystander PAD shock, n (%) [N=1410;1406;1437;4259]	66 (4.7%)	61 (4.3%)	61 (4.2%)
Bystander CPR, n (%) [N=1410;1406;1437;4259]	851 (60.4%)	801 (57.0%)	828 (57.6%)
Call time[2] to first EMS arrival in minutes, mean (sd) [N=1537;1539;1571;4653]	5.9 (2.6)	5.7 (2.5)	5.8 (2.6)
Call time[2] to first EMS arrival ≤ 4 min, n (%) [N=1537;1539;1571;4653]	330 (21.5%)	340 (22.1%)	358 (22.8%)
Call time[2] to first ALS arrival in minutes, mean (sd) [N=1526;1532;1563;4627]	8.2 (5.2)	8.2 (4.8)	8.2 (4.7)
Site, n (%) [N=1539;1541;1573;4659]			
A	148 (9.6%)	139 (9.0%)	135 (8.6%)
B	241 (15.7%)	241 (15.6%)	253 (16.1%)
C	104 (6.8%)	103 (6.7%)	105 (6.7%)
D	88 (5.7%)	85 (5.5%)	93 (5.9%)
E	10 (0.6%)	14 (0.9%)	13 (0.8%)
F	334 (21.7%)	354 (23.0%)	358 (22.8%)
G	25 (1.6%)	23 (1.5%)	24 (1.5%)
H	271 (17.6%)	268 (17.4%)	277 (17.6%)
I	118 (7.7%)	119 (7.7%)	115 (7.3%)
J	200 (13.0%)	195 (12.7%)	200 (12.7%)

ITT population

各群間のBaselineに明らかな差はない

Table S6. Outcomes by Treatment Group in the Intention-to-Treat Population[1]

	Amiodarone (N=1539)	Lidocaine (N=1541)	Placebo (N=1573)	Amiodarone vs Placebo Difference (95% CI) P	Lidocaine vs Placebo Difference (95% CI) P	Amiodarone vs Lidocaine Difference (95% CI) P
Survival to discharge, n (%) [N=1534;1531;1569]	291 (19.0%)	282 (18.4%)	276 (17.6%)	1.4% (-1.3%, 4.1%) P=0.32	0.8% (-1.9%, 3.5%) P=0.55	0.6% (-2.2%, 3.3%) P=0.70
MRS ≤ 3, n (%) [N=1531;1530;1568]	221 (14.4%)	207 (13.5%)	217 (13.8%)	0.6% (-1.9%, 3.0%) P=0.63	-0.3% (-2.7%, 2.1%) P=0.80	0.9% (-1.6%, 3.4%) P=0.47
Transported, n (%) [N=1539;1541;1573]	1166 (75.8%)	1187 (77.0%)	1229 (78.1%)	-2.4% (-5.3%, 0.6%) P=0.12	-1.1% (-4.0%, 1.8%) P=0.46	-1.3% (-4.3%, 1.7%) P=0.41
ROSC at ED arrival, n (%) [N=1539;1540;1573]	489 (31.8%)	545 (35.4%)	516 (32.8%)	-1.0% (-4.3%, 2.3%) P=0.54	2.6% (-0.7%, 5.9%) P=0.13	-3.6% (-6.9%, -0.3%) P=0.03
Admitted to hospital, n (%) [N=1539;1541;1573]	593 (38.5%)	632 (41.0%)	572 (36.4%)	2.2% (-1.2%, 5.6%) P=0.21	4.6% (1.2%, 8.1%) P=0.01	-2.5% (-5.9%, 1.0%) P=0.16

ITT population

←Primary

←Secondary

ITT解析でも
各群間でPrimary/Secondary Outcomeに有意な差はない

Table S7. Adverse Events[1] in the Intention-to-Treat Population[2]

ITT population

	Amiodarone (N=1539)	Lidocaine (N=1541)	Placebo (N=1573)	Overall P-value
Thrombophlebitis within 24 hours, n (%)	1 (0.1%)	3 (0.2%)	2 (0.1%)	0.60
Anaphylaxis with 24 hours, n (%)	0	0	0	NA
Clinical seizure activity within 24 hours, n (%)	50 (3.2%)	71 (4.6%)	57 (3.6%)	0.13
Pacing within 24 hours[3], n (%)	60 (3.9%)	42 (2.7%)	43 (2.7%)	0.10
IV/IO complications within 24 hours, n (%)	2 (0.1%)	1 (0.1%)	2 (0.1%)	0.82
Any nonfatal serious adverse event[4] within 24 hours, n (%)[5]	12 (0.8%)	15 (1.0%)	5 (0.3%)	0.07
Any nonfatal adverse event within 24 hours, n (%)[5]	112 (7.3%)	113 (7.3%)	101 (6.4%)	0.53
Death before discharge, n (%)	1243 (80.8%)	1249 (81.1%)	1293 (82.2%)	0.61
Any adverse event within 24 hours or death before discharge, n (%)	1284 (83.4%)	1278 (82.9%)	1314 (83.5%)	0.76

各群間で有害事象に明らかな差はない

考察

- 今研究ではアミオダロン、リドカインによる退院時生存率の上昇、神経学的予後の改善は認められなかった
- 過去の研究ではアミオダロンはリドカイン、Placeboと比較して短期予後(ROSC率と病院到着時の生存率)の改善が示された
- 今研究でもPlaceboに比較して同様に短期予後の改善は認めるもののアミオダロンとリドカインに差はなかった
- EMSコールから薬剤投与までの時間は平均19分と過去の研究よりは早いが、この投与までの遅れが、細胞障害(Metabolic phaseに至るため)による抗不整脈薬の効果を減衰させている可能性がある

考察

- 退院時生存率に差が出なかった原因について
  - そもそも抗不整脈作用がない→否定的
    -アミオダロン、リドカインはともにPlaceboに比較して除細動の回数が少なく、病院到着時の生存率が高い。入院後もCPRを要する率、他の抗不整脈薬を要する率が低い
  - 薬剤関連有害事象が生存率を減少させた→否定的
    -各群での有害事象の発生率に明らかな差はなかった
  - 入院後のケアに差があった→否定的
    -各群で冠動脈造影、TTM、蘇生終了までの時間などに明らかな差はなかった

考察

- 薬剤の効果は投与タイミング、患者の特徴に影響を受ける

  -witnessがある群で有意に治療反応性が高い傾向にある

  →witnessのある群での薬剤投与は有用

- 計画時の推定よりplacebo群の生存率が高い

  →パワー不足の可能性がある

-アミオダロン群のplacebo群に対する治療効果が3%であれば、検出力0.9で差を証明するためには計9000人の患者が必要となる
-3%の生存率の向上はすなわち1800人/年の命をアミオダロンが救う計算になる

Limitation

- Exclude群は非常に少なく、研究に参加しない場合の理由も追跡されているが、選択バイアスが存在する可能性はある

- 参加した患者の元々の生存確率が低く、実際の治療効果が現れにくかった可能性がある

結論

ショック抵抗性のVF/pVTによる

院外CPAにおいて

アミオダロン/リドカイン投与は

退院時生存率/神経学的予後を

改善しない

当院の見解

- Witnessの有無でアミオダロン/リドカインの治療効果が変わっていることから、早期の薬剤投与が望ましいのかもしれない
- 過去の研究ではアミオダロンはリドカインよりも優れているという結果だったが今研究では病院到着時の生存率に関しては明らかな差は認めず、自己心拍再開率についてはむしろリドカインの方が優れている傾向を認めた
- この原因は元来の薬理学的作用の差なのか偶然によるものなのかははっきりしない

当院の見解

- 今研究はパワー不足の可能性があり、今後より大規模な研究が行われるかもしれない
- しかし、これまで大規模studyの結果が出ているため倫理的な問題を孕んでいる
- 自らの治療方針は今まで通りAHA2015に則って行い、アミオダロンの投与はできる限り早めに行うよう心掛けるが、それ以上に質の高いCPRを心掛けたい