Clinical application of mild therapeutic hypothermia after cardiac arrest*

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Objective: **Postresuscitative mild hypothermia lowers mortality, reduces neurologic impairment after cardiac arrest, and is recommended by the International Liaison Committee on Resuscitation. The European Resuscitation Council Hypothermia After Cardiac Arrest Registry was founded to monitor implementation of therapeutic hypothermia, to observe feasibility of adherence to the guidelines, and to document the effects of hypothermic treatment in terms of complications and outcome.**

Design: **Cardiac arrest protocols, according to Utstein style, with additional protocols on cooling and rewarming procedures and possible adverse events are documented.**

Setting: **Between March 2003 and June 2005, data on 650 patients from 19 sites within Europe were entered.**

Patients: **Patients who had cardiac arrest with successful restoration of spontaneous circulation were studied.**

Measurements and Main Results: **Of all patients, 462 (79%) received therapeutic hypothermia, 347 (59%) were cooled with an endovascular device, and 114 (19%) received other cooling methods such as ice packs, cooling blankets, and cold fluids. The median cooling rate was 1.1°C per hour. Of all hypothermia patients, 15 (3%) had an episode of hemorrhage and 28 patients (6%) had at least one episode of arrhythmia within 7 days after cooling. There were no fatalities as a result of cooling.**

Conclusions: **Therapeutic hypothermia is feasible and can be used safely and effectively outside a randomized clinical trial. The rate of adverse events was lower and the cooling rate was faster than in clinical trials published. (Crit Care Med 2007; 35:●●●–●●●)**

KEY WORDS: cardiac arrest; cardiopulmonary resuscitation; hypothermia; induced; registries; intensive care; adverse effects

Postresuscitative mild hypothermia decreases mortality and reduces neurologic impairment after cardiac arrest. This association was reported by two randomized controlled trials (1, 2) and confirmed by meta-analysis (3). Therapeutic hypothermia is recommended by the International Liaison Committee on Resuscitation (ILCOR) (4). Recently, the European Resuscitation Council (ERC) recommended mild hypothermia for unconscious adult patients with restoration of spontaneous circulation after out-of-hospital cardiac arrest due to ventricular fibrillation, and the American Heart Association Advisory Committee for CRR suggested it as class IIa recommendation (5, 6).

The Hypothermia After Cardiac Arrest study group (HACA), after successful completion of its randomized controlled trial, reformed initially as the CoolHeart Registry in May 2003. By the beginning of 2004, the registry was brought under the auspices of the ERC and the name was changed to European Resuscitation Council Hypothermia After Cardiac Arrest Registry (ERC HACA-R). The ERC HACA-R was not designed to retest the hypothesis examined in the original HACA randomized controlled trial but to monitor developments in medical practice after the ILCOR recommendations on hypothermia in cardiac arrest were published.

This report is a descriptive overview of the first 650 cases entered into the ERC HACA-R. It reflects the state of the art in the use of hypothermia in the postresuscitation care of patients with cardiac arrest within Europe. Specifically, this study has used the ERC HACA-R to answer two questions. First, how is therapeutic hypothermia applied in daily clinical routine (e.g., is adherence to the guidelines feasible)? Adherence to the guidelines was defined by relevant deviances from the recommended time interval from return of spontaneous circulation (ROSC) to start of therapeutic hypothermia, cooling rate, target temperature, and rewarming rates. Second, what are the results of the use of therapeutic hypothermia, in terms of adverse events, survival rate, and neurologic outcome, outside the confines of a randomized controlled trial?

METHODS

Registry. The database used in this observational study was the ERC HACA-R. This cardiac arrest registry was open to licensed medical practitioners in Europe. It was operated in compliance with the European Directive on Privacy. All study sites followed Utstein recommended guidelines for cardiac arrest and cardiopulmonary resuscitation treatment and outcome reports (7, 8). In addition to the Utstein documentation, cooling intervention variables and the occurrence of any coagulopathy or arrhythmia as adverse events of cooling were recorded. Data entry was via a Web page–enabled data portal, and data entry was reimbursed by Alsius Corporation (Irvine, CA), but there was no sponsoring of the Alsius cooling device. Participating sites had control and responsibility for the integrity of their own data within the registry. The registry's

***See also p. 000.**

Dr. Arrich assumes overall responsibility for the integrity of the manuscript.

The Hypothermia After Cardiac Arrest Study Group investigators are listed in Appendix 1.

Alsius Corporation, Irvine, CA, was involved as observer in the design of the study, data management, and data analysis. Alsius Corporation was allowed to review the manuscript; however, any decisions regarding manuscript revision were made by the authors. The authors have not disclosed any potential conflicts of interest.

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study protocol was approved by the ethical review board of the Medical University of Vienna, Austria. Audits of source data were not conducted. In the first 7 months of data acquisition, only patients who were cooled with an endovascular cooling catheter could be entered in the registry. This was changed by the beginning of 2004, and the registry was opened for all patients with cardiac arrest.

Planning and approval of data analysis was by the steering committee of the ERC HACA-R (Appendix 1). Data analysis was planned after an arbitrary 500 patients had been entered into the database. All patients who had their cardiac arrest before June 30, 2005, were included in the analysis, and 4 months were allowed for follow-ups; the database was locked on November 12, 2005.

Data Collection. All patients who presented after cardiac arrest with ROSC were eligible for inclusion into the database, whether they received therapeutic hypothermia or not. At the beginning of the documentation, participating sites were asked to provide the following information: patients obeying verbal command after ROSC and before start of cooling, pathogenesis of cardiac arrest thought to be caused by trauma or severe bleeding, known coagulopathy (except therapeutically induced), known pregnancy, terminal disease, or do-not-attempt-resuscitation order. These criteria served as exclusion criteria for cooling. If one of these applied to a patient, their data were documented, but this patient was then excluded from the data analysis. The primary end point was the cooling protocol, including the interval from cardiac arrest and ROSC to initiation of cooling, the cooling rate, cooling duration, and rewarming rate. Secondary end points were the rate of coagulopathy and arrhythmia, in-hospital mortality, and good neurologic outcome to hospital discharge. Participating sites ranked patients according to three scales of neurologic and functional outcome: cerebral performance categories, overall performance categories, and the Glasgow Coma Scale (7–9). The best score reached and the final score before hospital discharge or death was documented.

Therapeutic Hypothermia. The decision to use therapeutic hypothermia and the choice of the cooling method was at the physician's discretion. The following recommendations were made but not mandated: cool unconscious patients after restoration of spontaneous circulation to 33 ± 1°C; reach the desired patient temperature as soon as possible; maintain at the target temperature for 24 hrs; rewarm to >36°C in ≥8 hrs; normothermia of <37.5°C should be maintained or achieved after rewarming. The recommendations could be found on the registry's Website (http://www.erchacar.org).

Data Analysis. Continuous data are presented using mean and SD or median and interquartile range (IQR), as appropriate; categorical data are presented using absolute frequencies. Comparisons between continuous variables were performed using chi-square statistics, Student's *t*-test, or Wilcoxon rank-sum test, as appropriate.

RESULTS

Between May 2003 and June 2005, data on 650 patients across 19 sites were entered (Appendix 1). A total of 63 patients were excluded from the data analysis according to the exclusion criteria. Reasons for the exclusion were: patient obeying verbal command after ROSC and before start of cooling (49 patients), pathogenesis of cardiac arrest thought to be caused by trauma or severe bleeding (six patients), known coagulopathy (four patients), and terminal disease or do-not-attempt-resuscitation order (four patients). One patient was obeying a verbal command and had coagulopathy. A descriptive analysis of baseline characteristics on the remaining 587 patients is presented in Table 1. The patients were predominately men (433 patients, 74%), with an average age of 60 yrs (SD 15). The majority had bystander-witnessed (531 patients, 90%), out-of-hospital (484 patients, 83%) cardiac arrest of cardiac origin (531 patients, 90%), with an initial rhythm of ventricular tachycardia/ventricular fibrillation (366 patients, 62%) and a median collapse to ROSC interval of 22 mins (SD 14–30). Specific cerebral performance categories and overall performance categories scores are provided in Table 2. A total of 279 patients (48%) died during hospital stay. Of these, 98 (35%) had severe hypoxic–ischemic encephalop-

Table 1. Descriptive analysis of collected data (n = 587)

	All Patients (n = 587)	Hypothermia (n = 462)	Normothermia (n = 123)	*p* Value
Demographics				
Age in years, mean ± SD	60 ± 15	59 ± 14	60 ± 16	.02
Female sex, n (%)	154 (26)	107 (23)	47 (38)	.01
Body mass index, mean ± SD	26 ± 4.8	26 ± 5	27 ± 5	.63
Details of cardiac arrest				
Location of cardiac arrest out of hospital, n (%)	484 (83)	419 (91)	65 (53)	<.001
Cause of cardiac arrest presumed cardiac, n (%)	446 (76)	377 (87)	67 (56)	<.001
Bystander witnessed cardiac arrest, n (%)	531 (90)	417 (90)	112 (91)	.47
Bystander CPR, n (%)	283 (48)	236 (51)	45 (37)	<.001
First cardiac rhythm ventricular fibrillation/tachycardia, n (%)	366 (62)	318 (68)	46 (37)	<.001
First cardiac rhythm asystole, n (%)	110 (19)	84 (18)	26 (21)	<.001
First cardiac rhythm PEA/EMD, n (%)	87 (15)	40 (8.7)	47 (38)	<.001
Time in minutes to initiation of bystander CPR, median (IQR)	4 (2–8)	5 (2–8)	3 (1–5)	.06
Time in minutes to call emergency medical services, median (IQR)	2 (1–5)	2 (1–5)	2 (1–5)	.74
Time in minutes to arrival of emergency vehicle, median (IQR)	10 (7–15)	10 (7–15)	8 (5–11)	.03
Time in minutes to first defibrillation, median (IQR)	10 (6–14)	5 (2–8)	3 (1–5)	.02
Time in minutes to arrival at emergency department, median (IQR)	60 (44–80)	61 (46–82)	46 (25–67)	<.001
Time in minutes to ROSC, median (IQR)	22 (14–30)	23 (16–32)	17 (5–25)	<.001
Outcome				
Unfavorable outcome, n (%)	334 (57)	250 (55)	84 (68)	.02
Died during hospital stay, n (%)	279 (48)	195 (43)	84 (68)	<.001

CPR, cardiopulmonary resuscitation; PEA/EMD, pulseless electrical activity/electromechanical dissociation; IQR, interquartile range; ROSC, return of spontaneous circulation.

Unfavorable outcome is defined by a cerebral performance categories score of >2 before hospital discharge or in-hospital mortality. Bystander CPR is strictly defined by basic life support from bystanders (mostly laymen); any advanced life support measures are not included.

Table 2. Specific outcome scales for all patients (n = 587), including patients who died during hospital stay

Score	Best		Final	
	OPC	CPC	OPC	CPC
1. Good overall/cerebral performance, n (%)	196 (33.4)	208 (35.4)	190 (32.4)	198 (33.7)
2. Moderate overall performance/disability, n (%)	57 (9.7)	51 (8.7)	58 (9.9)	55 (9.4)
3. Severe overall/cerebral disability, n (%)	48 (8.2)	44 (7.5)	45 (7.7)	38 (6.5)
4. Vegetative state, n (%)	186 (31.7)	190 (32.4)	169 (28.8)	171 (29.1)
5. Brain death, n (%)	29 (4.9)	29 (4.9)	45 (7.7)	45 (7.7)
Unknown, unassessable, n (%)	71 (12.1)	65 (11.1)	80 (13.6)	80 (13.6)

OPC denotes overall performance categories; CPC denotes cerebral performance categories.

Table 3. Temperature profiles of cooled patients (n = 465)

	n	Median	IQR
All cooling methods			
Time from collapse to initiation of cooling, mins	418	159	(96–244)
Time from ROSC to initiation of cooling, mins	434	131	(75–118)
Cooling rate after 1 hr, °C	394	1.1	(0.5–1.8)
Temperature at start of cooling, °C	410	35.5	(34.8–36.2)
Duration of cooling, hrs	416	24.3	(23.7–26)
Coldest temperature reached, °C	439	32.8	(32.4–33)
Duration of rewarming, hrs	391	9	(6.8–12)
Endovascular cooling			
Time from collapse to initiation of cooling, mins	326	175	(112–255)
Time from ROSC to initiation of cooling, mins	337	150	(94–226)
Temperature at start of cooling, °C	319	35.1	(34.6–36.2)
Cooling rate after 1 hr, °C	308	1.1	(0.6–1.7)
Duration of cooling, hrs	320	24.4	(24–26.1)
Coldest temperature reached, °C	339	32.9	(32.6–33)
Duration of rewarming, hrs	302	8.5	(6.8–11)
Any other cooling method (cold fluids, ice packs, surface cooling)			
Time from collapse to initiation of cooling, mins	92	98	(54–145)
Time from ROSC to initiation of cooling, mins	96	75	(26–130)
Temperature at start of cooling, °C	91	35.8	(35.3–35.6)
Cooling rate after 1 hr, °C	85	1.3	(0.4–2.0)
Duration of cooling, hrs	89	24.2	(23.5–25.3)
Coldest temperature reached, °C	100	32.4	(31–32.9)
Duration of rewarming, hrs	87	10.5	(7.8–18.5)

n, number of patients for whom information is available; IQR, interquartile range; ROSC, return of spontaneous circulation.

athy, 74 (27%) died of cardiogenic shock, 29 (10%) of arrhythmia or secondary cardiac arrest, 16 (6%) of sepsis, and 52 (18%) died of other causes. A total of 334 patients had an unfavourable outcome defined by a best cerebral performance categories score of >2 or death during hospital stay.

Cooling. Of all patients, 462 (79%) received therapeutic hypothermia. Of these, 347 (75%) were cooled with an endovascular device that consisted of a closed system of a femoral central catheter (ICY or Cool Line, Alsius Corporation) and an external heat exchange system; 114 (25%) were treated with another cooling method such as ice packs, cooling blankets, and cold fluids. Of all 19 sites, 13 used endovascular cooling, three used other cooling methods, and three used both. Temperature profiles for the cooled patients are provided in Table 3. The median time from collapse to initiation of cooling was 159 mins (IQR, 96–244 mins), the median time from ROSC to the initiation of cooling was 131 mins (IQR, 75–218 mins), the median cooling rate was 1.1°C per hour, and the coldest temperature reached was 32.8°C (IQR 32.4–33°C). Cooling profiles between patients who were cooled with the endovascular device or any other cooling method were similar except time to cooling and rewarming rates. From time to ROSC, it took 150 mins (IQR, 94–112 mins) to initiate endovascular cooling, whereas it took 75 mins (IQR, 26–130 mins) to initiate surface cooling or to administer cold fluids. The coldest temperature reached was with 32.4°C (IQR 31–32.9°C), significantly lower with all other cooling methods than with endovascular cooling (32.9°C; IQR, 32.6–33°C). The median time to normothermia was 8 hrs (IQR, 6.8–11 hrs) in the endovascular group and 10.5 hrs (IQR, 7.8–18.59 hrs) for patients who were cooled with any other method. All other parts of the cooling profile were similar.

Normothermia vs. Hypothermia. A total of 123 patients (21%) did not receive hypothermia. A descriptive analysis of the baseline characteristics of the normothermia patients and the hypothermia patients is provided in Table 1.

Normothermia vs. Hypothermia Among Patients with Pulseless Electrical Activity/Electromechanical Dissociation or Asystole as First Cardiac Rhythm and In-hospital Cardiac Arrest. Of the 101 patients with in-hospital cardiac arrest, 43 (43%) received therapeutic hypothermia; of 197 patients who had pulseless electrical activity/electromechanical dissociation (PEA/EMD) or asystole as first cardiac rhythm, 124 (63%) received therapeutic hypothermia (Tables 4 and 5). Cooling profiles were comparable with those of the full cohort. Time from collapse to initiation of cooling and time from ROSC to initiation of cooling was distinctively quicker for the in-hospital cohort when compared with the full cohort and slightly quicker for the PEA/EMD/asystole cohort. Within the PEA/EMD/asystole cohort, mortality was lower for patients who received therapeutic hypothermia when compared with the control group. For all other outcome variables, there was no clear difference between cooling groups.

Cooling Profiles of Former HACA Trial Sites and High-Enrolling Sites. Of all participating sites, we compared results of sites that were expected to be experienced in the application on therapeutic hypothermia with the results of all other sites. Six sites (001, 002, 003, 004, 008, 027) contributed 75% of the data (454 patients), and three sites (001, 002, and 004) that had participated in the preceding HACA trial contributed 50% (292 patients). High-enrolling sites less often used endovascular cooling than low-enrolling sites (69% vs. 92%, $p < .01$). There was no significant difference in the variables of the cooling profiles between sites experienced with hypothermia except for two: the time interval between ROSC and start of cooling was shorter at high-enrolling sites than low-enrolling sites (145 mins vs. 173 mins, $p = .026$), and former HACA trial sites had a cooling

Table 4. Outcome and temperature profiles of patients with in-hospital arrest (n = 101)

	Hypothermia (n = 43)	Normothermia (n = 58)	*p* Value
Outcome			
Unfavorable outcome, n (%)	31 (72)	41 (71)	.99
Died during hospital stay, n (%)	26 (61)	17 (40)	.30
			Median (IQR)
Temperature profiles of cooled patients			
Time from collapse to initiation of cooling, mins			95 (56–95)
Time from ROSC to initiation of cooling, mins			64 (30–119)
Cooling rate after 1 hr, °C			1.6 (0.7–1.9)
Duration of cooling, hrs			24.5 (24–30.5)
Coldest temperature reached, °C			32.8 (32.4–33)
Duration of rewarming, hrs			9 (6.0–15.0)

n, number of patients for which information is available; IQR, interquartile range; ROSC, return of spontaneous circulation. Unfavorable outcome is defined by a cerebral performance categories score of >2 before hospital discharge or in-hospital mortality.

Table 5. Outcome and temperature profiles of patients with pulseless electrical activity/electromechanical dissociation or asystole as first rhythm (n = 197)

	Hypothermia (n = 124)	Normothermia (n = 73)	*p* Value
Outcome			
Unfavorable outcome, n (%)	89 (81)	59 (81)	.977
Died during hospital stay, n (%)	79 (65)	59 (81)	.023
			Median (IQR)
Temperature profiles of cooled patients			
Time from collapse to initiation of cooling, mins			141 (78–210)
Time from ROSC to initiation of cooling, mins			115 (95–194)
Cooling rate after 1 hr, °C			1.4 (0.6–2)
Duration of cooling, hrs			24.3 (23.8–25.5)
Coldest temperature reached, °C			32.7 (32.1–33)
Duration of rewarming, hrs			9 (7.4–13.9)

n, number of patients for which information is available; IQR, interquartile range; ROSC, return of spontaneous circulation. Unfavorable outcome is defined by a cerebral performance categories score of >2 before hospital discharge or in-hospital mortality.

rate of 1.3°C per hour, whereas the cooling rate was 1°C per hour for the rest of the centers. There was no difference in mortality and rate of neurologic outcome between former HACA trial sites and high-enrolling sites compared with all other centers (data not shown).

Adverse Events. The Registry recorded the following adverse events: any event of arrhythmia during 7 days after cooling or hemorrhage (Table 6). Of all hypothermia patients, 15 (3%) had hemorrhage. Six of these needed specific treatment, and in five cases, therapeutic hypothermia was stopped as a consequence. Arrhythmias within 7 days of the initiation of therapeutic hypothermia were reported in 28 patients (6%). In all but one case, therapeutic hypothermia was stopped as a consequence. There were no reports of cooling-related deaths. The rate of hemorrhage or arrhythmias did not differ between high-enrolling and low-enrolling sites. Patients for whom therapeutic hypothermia was stopped as a result of a complication were rewarmed with a median rewarming rate of 8 hrs (95% confidence interval, 4.7–9.1).

Looking at adverse events with endovascular cooling and all other cooling methods, there was no significant difference for bleeding complications (4% vs. 1.8%, $p = .3$). More patients who were cooled with the endovascular device had any kind of arrhythmias than patients who received any other form of therapeutic hypothermia (7.2% vs. 0.9%, $p = .01$).

DISCUSSION

Our study has shown that therapeutic hypothermia is feasible in clinical practice, outside the confines of a randomized controlled trial, in several European sites. Endovascular cooling, cold fluids, and surface cooling were used to apply therapeutic hypothermia. In summary, therapeutic hypothermia could be applied according to the guidelines, regardless of the frequency of treated cardiac arrest patients. Within the confines of an observational study, outcomes compare with those of preceding controlled studies. Sites that participated in the former HACA trial and enrolled a lot of patients managed a faster initiation of cooling and seemingly faster cooling rates in the first hour. This might have been due to an established routine. It is also possible that it was due to the fact that these sites experienced with hypothermia more often used surface cooling and fluid cooling than other sites, which can be initiated sooner after cardiac arrest and have faster initial cooling rates than the endovascular device (Table 3). Therapeutic hypothermia seemed be implemented and worked equally effective both for sites experienced with hypothermia and those that were new to the therapy.

About half of all patients with PEA/EMD or asystole as the first cardiac rhythm and half of those with in-hospital cardiac arrest received therapeutic hypothermia. These subgroups of patients lay beyond the inclusion criteria of the ILCOR recommendations. For both subgroups, time to cooling, cooling, and rewarming rates were comparable with the rest of the cohort. Outcome of cooled patients with PEA/EMD/asystole seemed to be better than for those with PEA/EMD/asystole who were not cooled, but there was no significant difference in the in-hospital subgroup. The inevitable selection bias for those patients included in the registry means that no firm conclusions can be made; however, there was no evidence of harm caused by cooling in this group.

Looking specifically at patients whose final neurologic outcome would be defined as vegetative state, 41% in the hypothermia group and 50% in the normothermia group had a cerebral performance categories score of 4 or 5 (difference not statistically significant). Also, here the registry design does not allow for any definitive inference, but at least it seems that hypothermia treatment did not result in an extensive proportion of patients in vegetative state.

The rate of the documented adverse events arrhythmia and bleeding was lower when compared with the preceding randomized controlled trials. Surprisingly, the bleeding rate did not differ between endovascular cooled patients and

Table 6. Adverse events of cooling (n = 462)

	Documented Adverse Events (n = 43)	Treated (n = 6)	Kind of Treatment	Cooling Stopped (n = 29)
Hemorrhage, according to bleeding sites				
Total number of events (%)	15 (3)	6		
Nose, n (%)	4 (1)	2	Surgical treatment	
Vagina, n (%)	0			
Subcutaneous tissue, n (%)	2 (0.4)			2
Deep muscle, n (%)	0			
Skin of legs or arms, n (%)	0			
Intracerebral, n (%)	0			
Urinary tract, n (%)	0			
Gastrointestinal, n (%)	2 (0.4)	2	Platelet infusions coagulations factors	1
Joint spaces, n (%)	0			
Mucous membranes, n (%)	1 (0.2)			
Intraabdominal, n (%)	0			
Insertion site, n (%)	5 (1)	2	Surgical treatment unknown	2
Mouth, n (%)	1 (0.2)			
Arrhythmias within 7 days after cardiac arrest				
Total number of events (%)	28 (6)			
Unknown, n (%)	6 (1)			6
Ventricular fibrillation, n (%)	12 (3)			10
Pulseless ventricular tachycardia, n (%)	8 (2)			7
Asystole, n (%)	0			
PEA/EMD, n (%)	1 (0.2)			1

PEA/EMD, pulseless electrical activity/electromechanical dissociation.

surface/fluid cooled patients, but there was a significantly higher amount of arrhythmias for the endovascular group than for patients receiving any other cooling method (7.2% vs. 0.9%, $p = .01$). We do not have an explanation for this observation.

There were no additional reports of adverse events related to any of the used cooling devices. Cooling catheters were removed after a mean of 51 hrs (SD 33 hrs), as it was often used for fever control after hypothermia treatment.

Strengths and Limitation of the Study. As this report relates to a registry, our study can provide qualitative information about progress in the use of mild hypothermia during postresuscitation care of survivors of cardiac arrest. The power of the data to provide comparative results is limited. Population-based inclusion of patients could be confirmed for only four sites (001, 003, 004, 026). As these sites contributed only 58% of all patient data, the presence of selection bias in the full cohort is likely. A recent review compared the data documentation of a randomized controlled trial on beta blockers in the treatment of heart failure with data documentation of subsequent community-based clinical registry and found significant differences in included patients (10). The application of ILCOR recommendations for the use of mild therapeutic hypothermia was proposed but not mandatory or controlled. During the period of data collection, most sites were only just starting to implement therapeutic hypothermia. It is possible that the decision to cool patients was influenced or delayed by several factors, such as presumed prognosis of the patient, costs of cooling devices, logistics, and further diagnostics and therapy such as a computer tomography or angiography.

The majority of sites cooled with the endovascular device, but there was also a sufficient number of patients who were cooled with other methods like cold fluids and surface cooling. Looking at the cooling profiles, the different methods were generally equally effective. The time to initiation of cooling was significantly longer in the endovascular cooling group, which is most likely due to the fact that other methods like surface cooling and cold fluids can be started much earlier, often even before the patient was admitted to hospital, whereas endovascular cooling is initiated after admission. On the other hand, there might have been a better temperature control with endovascular cooling. With surface cooling and fluid cooling, the median coldest temperature reached decreased with its confidence interval below the recommended 32°C, whereas it stayed around the recommended 32–34°C with endovascular cooling. Similar with endovascular cooling, it was possible to rewarm patients in 8.5 hrs and stick closely to the recommended 8 hrs, whereas it took 10 hrs with other cooling methods.

One possible criticism came from the beginning of data collection. During the first 9 months of patient enrollment, it was not clearly pronounced that the registry was for all cardiac arrest patients and not only the ones who were cooled with the endovascular device of the sponsor. In fact, participating sites did not make restrictions from the beginning on. Of the 87 patients who were enrolled during the first 9 months, 50% were cooled (79% in the full cohort). Among the hypothermia patients, 20% were cooled with other cooling methods than the endovascular device, which corresponds to the 25% in the full cohort.

One of the major limitations of HACA-R is that data entry was not controlled, and accurate data entry cannot be guaranteed for the full data set. There are arguments that indicate that this did not lead to relevant problems for the main results: data were monitored in terms of completeness and plausibility by the registry coordinator. About 50% of all data were documented by sites that participated in the previous HACA trial (1) and were experienced in accurate data documentation. The data set is coherent and results compare with previous literature.

Outside the confines of a randomized controlled trial, ERC HACA-R has proven to be a suitable monitor for the use of therapeutic hypothermia at multiple sites in Europe. Besides the results of a randomized controlled trial, experiences with registry data are important for everyday clinical practice. It allowed inferences of patient subgroups whose indications lay beyond the inclusion criteria of the preceding randomized controlled trials and ILCOR recommendations.

Our Results in Comparison with the Existing Literature. Following up on the preceding randomized controlled trials and recommendations by ILCOR, the interval between ROSC to initiation of cooling was 159 mins in HACA-R, which was longer than the median 105 mins re-

ported by the HACA trial study group (1). However, the cooling rate of 1.1°C per hour observed in HACA-R was distinctively faster than the median cooling rate of 0.3°C during HACA trial and a little faster than the cooling rate of 0.9°C per hour reported by Bernard et al. (2). Studies where solely cold fluids were used for the initiation of therapeutic hypothermia reported faster cooling rates, between 1.1°C and 1.7°C within the first 30 mins, but in all studies, additional cooling methods had to be added after the completion of fluid administration (11, 12). Using fluid cooling and additional methods may combine the advantages of rapid and easy induction and accurate maintenance of therapeutic hypothermia.

Hypothermia was maintained for a median of 24.3 hrs (IQR, 23.7–26 hrs). The median time to normothermia was 9 hrs (IQR, 6.8–12 hrs). Both are in accordance with the ILCOR recommendations (4).

In our study, adverse events were recorded only for patients who received therapeutic hypothermia. Hemorrhage was reported for 3% of all patients who received therapeutic hypothermia, arrhythmia within 7 days after cardiac arrest was reported for 6%. The rate of adverse events was lower than in the HACA trial (1), which reported that in the hypothermia group, 26% experienced any kind of bleeding and 36% had any kind of arrhythmia 7 days after cardiac arrest. Neither in the HACA trial nor in the trial by Bernard et al. (2) could a statistically significant difference between treatment group and the control be found.

Both randomized controlled trials and a meta-analysis (3) showed that therapeutic hypothermia resulted in a significant neurologic benefit for patients after cardiac arrest. Patients receiving therapeutic hypothermia were more likely to be alive with a good neurologic outcome after 6 months than those in the control group (risk ratio, 1.44; 95% confidence interval, 1.11–1.76) (3). In our analysis, we observed a risk ratio of 1.41 (95% confidence interval, 1.08–1.89) for being alive with good neurologic outcome in the normothermia group, which compares with the result in the meta-analysis.

Implication of Results. As a relatively new therapeutic concept, many questions concerning an optimal cooling protocol for cardiac arrest patients have yet to be answered. In the future, the registry may show systematic problems with the use of therapeutic hypothermia and enable suggestions to be made for modifying the cooling protocol and cooling methods. These amendments could then serve as basis for a randomized controlled trial to further improve the effectiveness of therapeutic hypothermia.

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APPENDIX 1

European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group

The European Resuscitation Council (ECR) Hypothermia After Cardiac Arrest (HACA) Registry Steering Committee members are: Fritz Sterz, MD, PhD, Department of Emergency Medicine, University of Vienna, Austria, and European Resuscitation Council (Chairman); Risto O. Roine, MD, PhD, Turku University Central Hospital, Finnland; Kjetil Sunde, MD, PhD, Ulleval University Hospital, Oslo, Norway; Jerry Nolan, MD, Royal United Hospital, Bath, UK; Leo Bossaert, MD, European Resuscitation Council; and Jasmin Arrich, MD (Registry Cocoordinator), Department of Emergency Medicine, University of Vienna, Austria.

The following investigators participate in the Hypothermia After Cardiac Arrest Registry (HACA-R) Study Group (the number of patients enrolled at each center is shown):

Steering Committee: Fritz Sterz, MD, PhD (site 001, Universitätsklinik für Notfallmedizin Vienna, Austria; n = 191), Risto O. Roine, MD, PhD (site 002, Helsinki University Central Hospital, Finland; n = 63), Kjetil Sunde, MD, PhD (site 003, Ulleval University Hospital Oslo, Norway; n = 87), Leo Bossaert, MD (European Resuscitation Council), Jerry P. Nolan, MD (site 020, Royal United Hospital Bath, UK; n = 11), and Ken Collins, MD, PhD (Observer, Alsius Corporation).
Statistical Evaluation: Joel Verter, PhD, and Judy Bebchuk, ScD (Statistics Collaborative, Washington, DC).
Hospital Investigators: Gaetan Beduneau (site 021, Reanimation Medicale CHU Rouen, France; n = 5), Bas Bekkers, MD (site 015, University Hospital Maastricht, The Netherlands; n = 1),

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