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Eligibility for Extracorporeal Cardio-Pulmonary Resuscitation in Out-of-Hospital Cardiac Arrests in Sweden

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ABSTRACT

Background: Extracorporeal Cardio-Pulmonary Resuscitation (ECPR) can potentially enhance outcomes following out-of-hospital cardiac arrest (OHCA). Selection criteria determine candidacy for ECPR and affect outcomes, as do numbers of ECPR treatments per centre. The objective of this study was to evaluate ECPR eligibility amongst witnessed OHCA in Sweden, by means of the Swedish Registry for Cardiopulmonary Resuscitation.

Method: Data of witnessed OHCA was extracted from the registry between Jan 2015 and Aug 2019. Evaluation of ECPR-candidacy was based on selection criteria and transport time. Treatment was considered contraindicated if no-flow time extended beyond 5 min. Two groups were defined: Group Restrictive (GR); 18–65 years of age with shockable rhythm and Group Liberal (GL); 18–70 years of age, independent of rhythm. Emergency medical services stations of corresponding OHCA was plotted on a map and time of transportation calculated. Maximum time for transportation was set to 40 min.

Results: Out of 15,911 witnessed OHCA, 6372 were considered ECPR-ineligible due to extended no-flow time. GR constituted of 1519 and GL 5851 OHCA. Cases with return of spontaneous circulation at admission were subtracted from both groups. The remaining OHCA in GR (636) and GL (3558) were considered ECPR-candidates. After excluding cases due to extended time of transport, 218 and 1246 candidates remained ECPR-eligible in GR and GL respectively.

Conclusion: The quantity of ECPR-eligible patients amongst OHCA is highly dependent on selection criteria and geographics. In Sweden, we estimate an annual incidence of 46–267 potential candidates per 10.5 M inhabitants, corresponding to 1.4%–7.8% of all witnessed OHCA.

Editorial Comment: This analysis of the national database for out of hospital cardiac arrest in Sweden from a selected period uses case characteristics to estimate how many might be eligible for extra-corporeal cardiopulmonary resuscitation given today's criterial for this type of treatment.

1 | Introduction

There has been an increasing interest in the use of extracorporeal cardiopulmonary resuscitation (ECPR) on refractory cardiac arrests to improve outcomes. Observational studies have shown improved survival to hospital discharge and improved neurological outcome when ECPR is compared to traditional resuscitation in out-of-hospital cardiac arrests (OHCA). ECPR has become known to the public, which has raised political interest and, as a result, made fundings more available. Increasingly more centres are starting up [1] and experienced ones report exponentially more patients being treated, with superior outcomes compared to conventional cardiopulmonary resuscitation [2–4]. On the contrary, some centres report unchanged

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levels of survival after the implementation of ECPR-programs [5]. Randomized controlled trials on ECPR versus standard of care have emerged and are presenting conflicting results [6, 7]. ECPR-programs are resource intensive, which makes the establishment of such programs complex.

It is bothersome that the rate of survival has barely improved over time [8], and there are still many issues that need to be further investigated in order to ameliorate outcomes. Selection criteria for treatment is one of them. Obviously, inclusion and exclusion criteria will not only affect outcomes but also the numbers available for ECPR.

In densely inhabited metropolitan areas, one can assume there is a sufficiently large cohort of candidates to justify an ECPR program. In sparsely inhabited areas, like larger parts of Sweden, the assumption cannot as easily be made. The potential incidence for ECPR eligibility in Sweden is not known. An estimate of potential ECPR candidates is crucial in order to assess national conditions for ECPR programs, not least when allocating meagre medical resources.

The objective of this study was to evaluate ECPR-eligibility amongst witnessed OHCA in Sweden, by means of the Swedish Registry for Cardiopulmonary Resuscitation (SCCR), to illustrate the prerequisites for a national ECPR program.

2 | Methods

This study was approved by the Swedish Ethical Review Authority (2019-03448) and funded by Uppsala University.

2.1 | Data Source

The SCRR started in 1990. It is an open registry including the vast majority (98%) of all resuscitation attempts in Sweden. Data input is made online by the resuscitators and validated by controllers. Registry data provides information on the cardiac arrest for 98% of Sweden's hospitals and the regions of the ambulance service. The registry aims to monitor and improve the links in the chain of survival.

Data of witnessed OHCA between January 1, 2015 and August 30, 2019 (56 months/4.67 years) was extracted from SCRR. Time of sampling was justified by coherent data during the time period and changes in the input of data made to the registry before and after. The OHCA cohort was described by age, sex, geographical location of the cardiac arrest, and the identity number of the Helicopter Emergency Medical Service (HEMS) or Emergency Medical Service (EMS) responding to the alarm. Detailed information on the resuscitation, such as the time of the cardiac arrest (if specified, otherwise the call to the dispatch centre was used as a surrogate), primary rhythm, cardiopulmonary resuscitation (CPR) prior to EMS arrival, termination of resuscitation (TOR) prior to hospital arrival, occurrence of incipient return of spontaneous circulation (ROSC), ROSC on hospital arrival, neurologic function as described by cerebral performance category (CPC) 1 or 2 at discharge from the hospital, and survival at 30 days were collected.

2.2 | Selection of Study Groups

All consecutive patients with witnessed OHCA between January 1, 2015 and August 30, 2019 were included in the study. Only cases with all information needed for the analysis available were evaluated for ECPR candidacy. Treatment with ECPR was considered contraindicated if no-flow time exceeded 5 min. Two arbitrary groups were determined based on commonly used criteria for ECPR and named Group restrictive (GR): 18–65 years of age with first recorded shockable rhythm (i.e., pulseless ventricular tachycardia or ventricular fibrillation) and Group liberal (GL): 18–70 years of age, independent of first recorded rhythm. All OHCA defibrillated by EMS crew or public semi-automatic device (AED), were considered as pulseless ventricular tachycardia or ventricular fibrillation. Only hospitals in Sweden with cardiothoracic surgical services available ($n = 8$), were considered "ECPR-capable". Patients presenting with ROSC at hospital arrival were excluded. EMS stations beyond 40 min of transport from an ECPR-capable hospital were excluded, except for all HEMS stations. Calculations of ECPR eligibility was based on assessment on hospital arrival.

2.3 | Outcome Measures

The primary outcome was the number of patients with witnessed OHCA in Sweden, potentially considered ECPR-eligible between January 1, 2015 and August 30, 2019. The study reports national and regional geographical distributions of ECPR-eligible OHCA, and numbers of EMS stations within reach of an ECPR-capable hospital.

To assess our estimates on time for transportation, we used local EMS- and hospital medical records from the Region of Uppsala, that is, catchment area for Uppsala University Hospital. The precise geographical location and actual time of transport to Uppsala University Hospital of all ECPR-eligible OHCA were thus obtained. The aetiology of each OHCA was investigated through findings in medical records.

2.4 | Statistical Methods

All statistical analyses were performed using R v 3.4.0. Categorical variables were presented as numbers with percentages in brackets. Continuous variables were presented as median with range in brackets, unless otherwise specified.

3 | Results

3.1 | Patient Selection

Out of a total of 15,911 witnessed OHCA, 6372 cases were deemed ECPR ineligible due to no-flow times exceeding 5 min, Figure 1. The remaining 9540 cases were divided into GR: 1519 and GL: 585, according to previously described selection criteria. In GR and GL, 883 and 2993 cases respectively, presented with ROSC at hospital admission and were considered ECPR ineligible. Remaining cases were considered potential candidates for ECPR, constituting 636 cases in GR and 3558 in GL. When excluding cases not able to reach an ECPR-capable hospital within

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the set time limit, 218 and 1246 patients remained eligible for ECPR in GR and GL respectively. After dividing the numbers by the time period of the study, it resulted in an annual ECPR-eligible cohort of 46–256 candidates, equal to 0.44–2.44 candidates per 100,000 inhabitants (population of 10.5 million).

The effects of conventional CPR on the study groups are depicted in Table 1.

3.2 | Geographical Impact on ECPR-Eligibility

The monthly regional distribution of ECPR-eligible patients in each group is presented in Figure 2 and ranged from 0.2–6 patients in GR to 0.9–24 patients in GL.

There were 65 EMS/HEMS units geographically situated within 40 min of transportation from an ECPR-capable hospital. Each

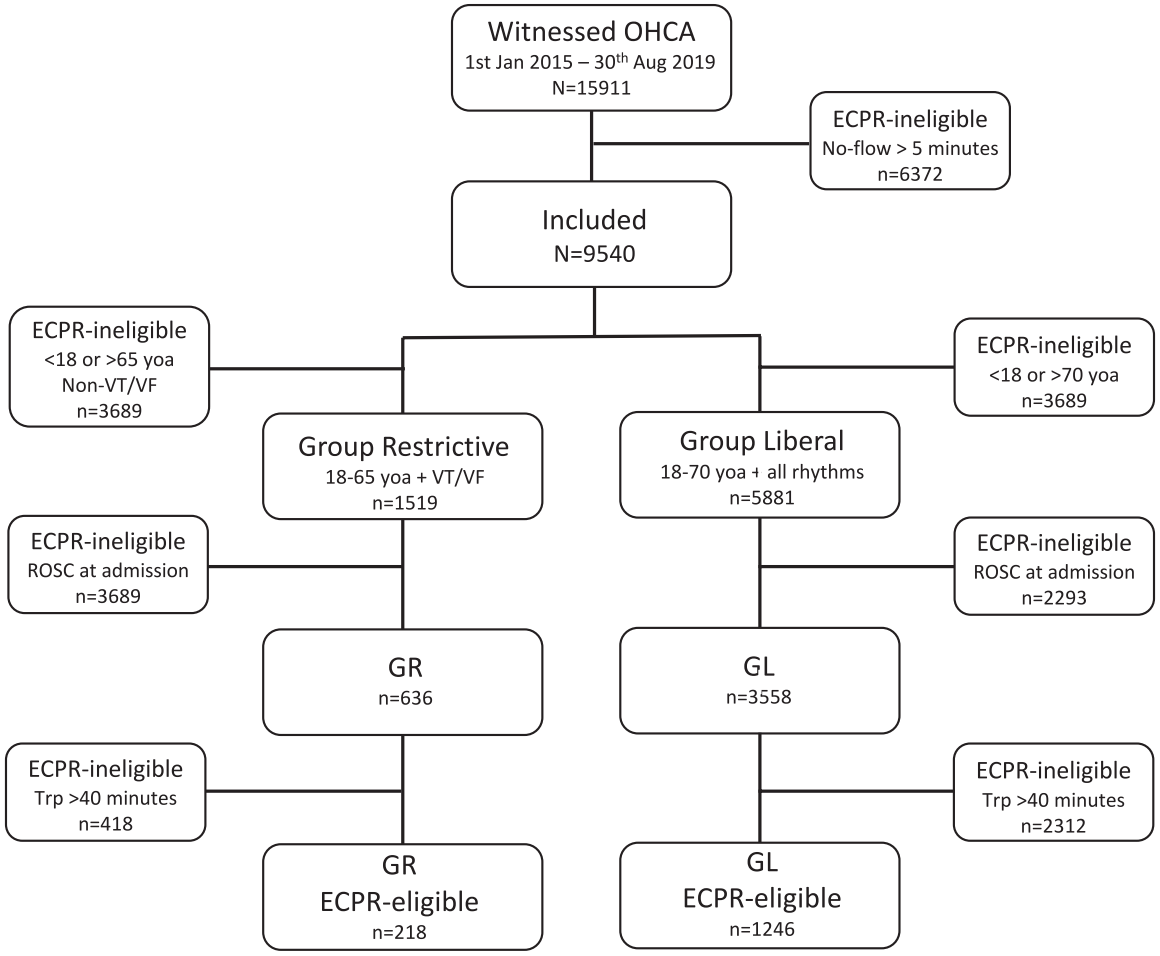

FIGURE 1 | Flow-chart for selection of candidates for ECPR amongst witnessed OHCA.

TABLE 1 | Characteristics and outcome of conventional CPR treatment ($n = 15{,}911$).

	Restrictive		Liberal	
	***n* (%)**	**Age**	***n* (%)**	**Age**
Size of cohort/median age/range	1519 (100)	52 (18–65)	5851 (100)	52 (18–70)
Male	1148 (76)		3818 (65)	
Bystander CPR prior to EMS arrival	1072 (71)		3803 (65)	
TOR prior to hospital admission	36 (2)		232 (4)	
Incipient ROSC	1029 (68)		2882 (49)	
ROSC at hospital arrival	883 (58)		2293 (39)	
CPC 1 or 2 at discharge from hospital	535 (35)		906 (15)	
30-days survival/median age/range	606 (40)	50 (18–65)	1036 (18)	52 (18–70)

Abbreviations: CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ROSC, return of spontaneous circulation; TOR, termination of resuscitation.

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hospital was served by 2–27 EMS/HEMS units, Table 2, and Figure 2.

In GR, 34% (218/636) of all ECPR candidates were handled by an EMS/HEMS unit within reach of an ECPR-capable hospital, and in GL, 35% (1246/3558).

3.3 | Subgroup Analysis of the Region of Uppsala

In a subgroup analysis of OHCA patients eligible for ECPR in the Region of Uppsala, 86% in GR and 45% in GL had a cardiogenic aetiology. OHCA in the Uppsala Region who were presumed to be within 40 min range of transport to Uppsala University Hospital were confirmed to be so in 77% of all cases Figure 3.

4 | Discussion

The main finding of this study is that the potential cohort of ECPR candidates amongst witnessed OHCA in Sweden ranges from 46–256 patients (0.44–2.44/100,000 inhabitants) per year, depending on the strictness of inclusion. Geographical location of the OHCA is a major determinant of ECPR availability.

4.1 | Selection Criteria

Selection criteria for ECPR are either remnants from research on conventional CPR or the product of retrospective studies on outcomes after ECPR. Often used criteria are age, time of no-flow, time of low-flow, that is, CPR, first recorded rhythm, biochemical and physiological markers such as pH, arterial blood lactate, and end-tidal carbon dioxide, and perhaps most important, any signs of life at the time of decision. There are ELSO recommendations on selection criteria [9], but no international consensus. Inclusion and exclusion criteria differ widely between centers.

In this study, there was a need to comply with information available in the registry when deciding on selection criteria. Criteria available were time of no-flow, age, and first recorded rhythm.

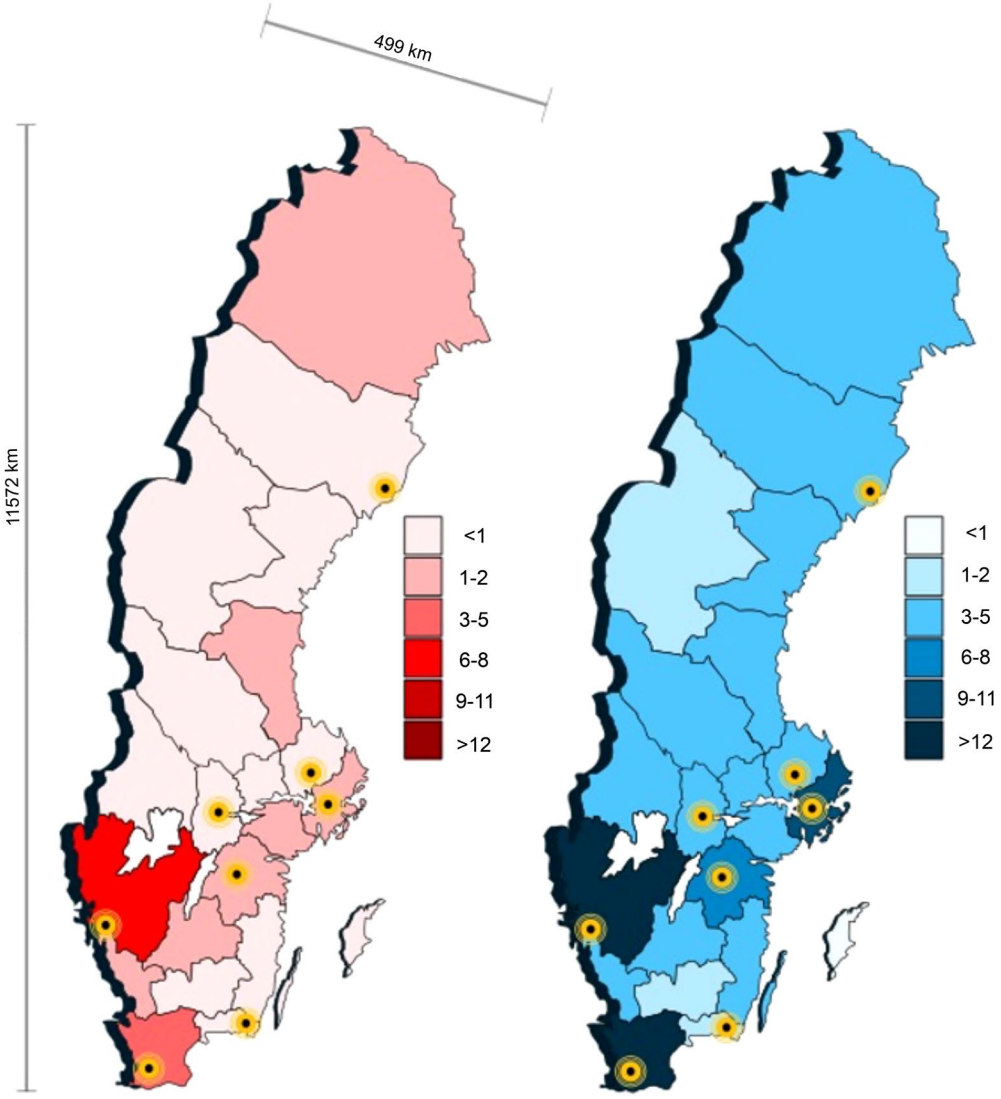

FIGURE 2 | The monthly regional incidence of ECPR candidates in GR (red) and GL (blue), independent of time of transportation. ECPR-capable hospitals are marked with yellow and black dots.

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TABLE 2 | Annual numbers of OHCA and EMS-stations within 40 min of transport from an ECPR-capable hospital.

ECPR-capable hospital	Restrictive	Liberal	(H)EMS-stations
	n	*n*	*n*
Karolinska University Hospital, Stockholm	12	62	27
Norrlands University Hospital, Umeå	2	10	2
Blekinge Regional Hospital, Karlskrona	0	7	2
Sahlgrenska University Hospital, Göteborg	13	70	14
Skåne University Hospital, Lund	8	43	7
Linköping University Hospital	4	32	4
Örebro University Hospital	3	17	5
Uppsala University Hospital	4	27	4
Nationally	47	267	65

Abbreviations: ECPR, extra-corporeal membrane oxygenation cardiopulmonary arrest; EMS, emergency medical service; OHCA, out of hospital cardiac arrest.

Although they can be considered arbitrary, they are recurrently used by other authors as well as in clinical practice [9–12] and are often found to be decisive for outcome in ECPR [2, 4]. As the optimal selection criteria for ECPR are not yet known, the decision was made to describe the ECPR-eligible cohort ranging from what could be considered "restrictive" to "liberal." It is apparent that the selection criteria have had a profound effect on numbers available for ECPR. Indeed, it is crucially important to know to what extent it affects ECPR-candidacy, as it is established that too few annual cases per center can impair outcome [13].

Only witnessed OHCA were included to be able to determine time of no-flow. Unwitnessed cardiac arrest and no-flow time exceeding 10 min is associated with a very poor prognosis [14]. In a study by Murakami et al. [15] the optimal cut-off value of no-flow time to predict favorable neurological recovery was 5 min. Cases exceeding a no-flow time of more than 5 min were excluded in this study.

Age limits in ECPR are a matter of recurrent discussion. ECPR for OHCA in infants and children is rarely attempted as they are primarily caused by non-cardiogenic factors and thus not suitable for ECPR [16, 17], but probably also because it is even more technically demanding than ECPR in adults. The upper age limit is debated, but studies on outcomes following ECPR favor younger patients [18, 19].

Shockable rhythms have consistently been associated with favorable neurologic outcome and improved survival in the ECPR-setting [8, 9, 20]. The prognosis is very poor if the primary rhythm is asystole [3, 19] and the literature is inconclusive concerning pulseless electric activity. In the Swedish EMS system, there are few physicians working in the prehospital setting. Most interpretations of first recorded rhythms are made by AEDs, defining only shockable or non-shockable rhythms, which is why the study groups were selected accordingly.

4.2 | Geographical Considerations

Sweden is geographically a long nation of 1572 km, with a population of 10.5 million people. The majority live in the lower one-third of the country and along the eastern coast. Hence, the regional occurrence of OHCA varies considerably. In Sweden, only a few hospitals offer ECPR for OHCA, and there are no national directives for treatment. As this study aims to investigate national conditions for ECPR among OHCA, only hospitals with cardiothoracic services have been considered ECPR-capable. These hospitals are foremost university hospitals, geographically distributed according to the number of inhabitants in the different regions. It is apparent that transport distances can be very long when suffering an OHCA in Sweden.

We decided on 40 min as the upper time limit of transportation for ECPR. We reason that previous studies have defined the optimal time of transit from conventional CPR to transport for intra-hospital ECPR, to approximately 16 min [19]. Prior to this should the cardiac arrest probably not be considered refractory [21]. Internationally, survival and neurologic outcome after ECPR drop if circulation is restored on ECMO only after 60 min of low-flow [22–24]. However, random cases of successful resuscitations after 100 min of low-flow have been described [25]. Time of decision-making and cannulation when arriving in hospital has been completely disregarded in this study. This means that the actual time from OHCA to ECPR has been allowed to exceed 60 min.

After excluding ECPR-candidates with transport times exceeding 40 min, approximately 2/3 in both groups remained ECPR-eligible. In the subgroup analysis of the Region of Uppsala, our estimate of time of transport was found to be correct in 77% of all cases, suggesting a lower availability to ECPR than calculated.

4.3 | Limitations

Firstly, the retrospective nature of a registry-based study presents obvious limitations. However, SCRR is a frequently used register for scientific research, with multiple annual publications in reputable journals.

Secondly, the methods used in this study can result both in an over- and underestimation of ECPR-eligibility. It is reasonable to argue that several of the candidates found eligible in this

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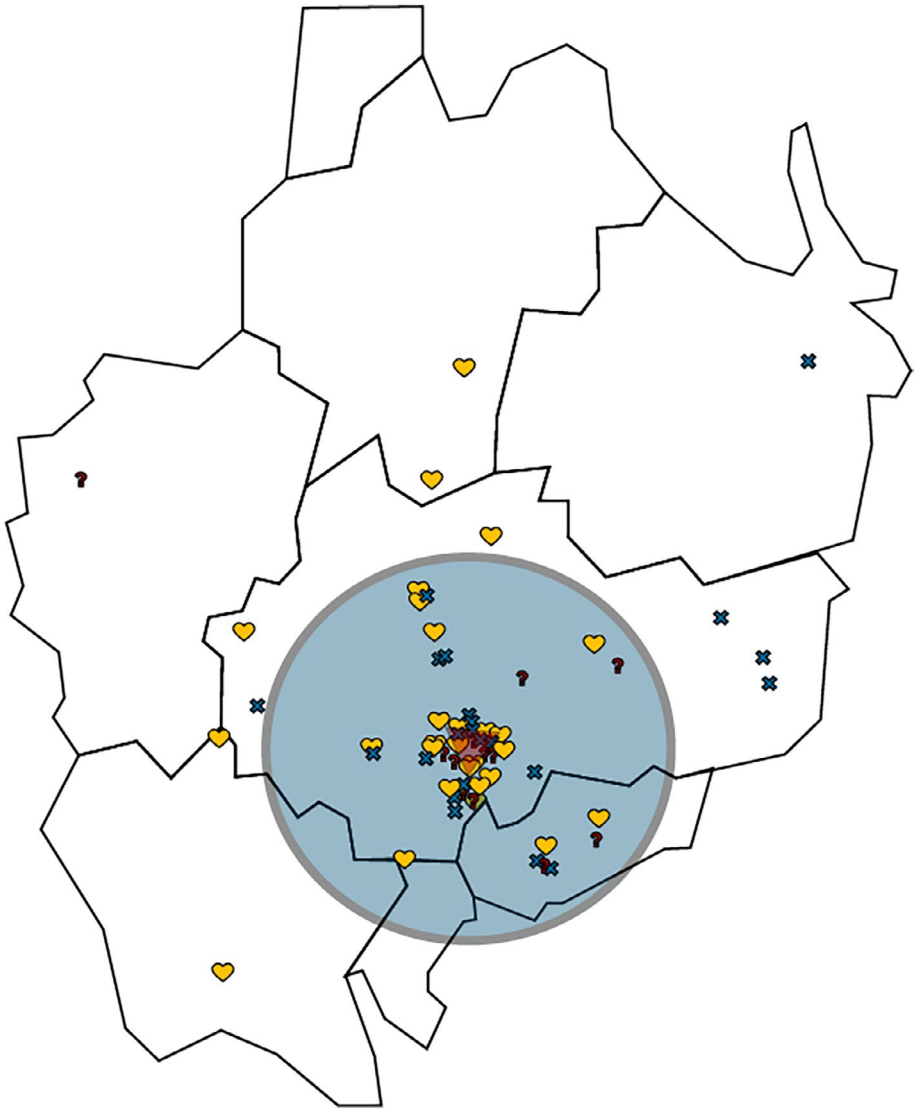

FIGURE 3 | ECPR-candidates in the region of Uppsala during the entire study period. The geographical location of each individual CA-alarm is described. The circle corresponds to 40 min of transport. Circulatory arrests of cardiogenic aetiology are marked with a heart, non-cardiogenic with a cross, and unknown with a question mark.

study would have been excluded in a real-life scenario, due to prolonged times of low-flow and significant co-morbidities not known to the investigators. On the other hand, underestimation of the ECPR-cohort is likely due to exclusion of patients with missing data for evaluation of ECPR-candidacy. Also, the time of transport is based on the geographical location of the reporting EMS station rather than the cardiac arrest, which adds to the uncertainty of our findings, as shown by our subgroup analysis of the Region of Uppsala.

Finally, deviations from ILCOR guidelines on CPR cannot be excluded.

5 | Conclusion

The quantity of ECPR candidates amongst witnessed OHCA is highly dependent on selection criteria and geographics. In Sweden, we estimate 1.4%–7.8% of all witnessed OHCA to be potential ECPR candidates, on average corresponding to 4–22 OHCA per month, nationwide. Only a minority of Swedish University Hospitals have a population base of ECPR-eligible patients amongst OHCA large enough to justify an ECPR program.

Author Contributions

All authors have made substantial contributions to the conception and design of this study as well as acquisition, analysis, and interpretation of data. All authors have contributed to the intellectual content as well as drafting of the article. The submitted version of this article has been unanimously approved by all authors, who accept accountability for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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