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The Pre-Hospital Fibrinolysis Experience in Europe and North America and Implications for Wider Dissemination

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Montreal, Quebec; Toronto, Ontario; Edmonton, Alberta; and Dalhousie, Nova Scotia, Canada; London and Swansea, United Kingdom; Vienna, Austria; Linköping and Stockholm, Sweden; Houston, Texas; and Paris, France

Objectives The primary objective of this report was to describe the infrastructures and processes of selected European and North American pre-hospital fibrinolysis (PHL) programs. A secondary objective is to report the outcome data of the PHL programs surveyed.

Background Despite its benefit in reducing mortality in patients with ST-segment elevation myocardial infarction, PHL remained underused in North America. Examination of existing programs may provide insights to help address barriers to the implementation of PHL.

Methods The leading investigators of PHL research projects/national registries were invited to respond to a survey on the organization and outcomes of their affiliated PHL programs.

Results PHL was successfully deployed in a wide range of geographic territories (Europe: France, Sweden, Vienna, England, and Wales; North America: Houston, Edmonton, and Nova Scotia) and was delivered by healthcare professionals of varying expertise. In-hospital major adverse outcomes were rare with mortality of 3% to 6%, reinfarction of 2% to 5%, and stroke of <2%.

Conclusions Combining formal protocols for PHL for some patients with direct transportation of others to a percutaneous coronary intervention hospital for primary percutaneous coronary intervention would allow for tailored reperfusion therapy for patients with ST-segment elevation myocardial infarction. Insights from a variety of international settings may promote widespread use of PHL and increase timely coronary reperfusion worldwide. (J Am Coll Cardiol Intv 2011;4:877–83) © 2011 by the American College of Cardiology Foundation

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Timely reperfusion through the administration of fibrinolytic therapy (FL) or primary percutaneous intervention (PCI) is critical in the management of acute myocardial infarction with ST-segment elevation (1,2). Compared with in-hospital administration, pre-hospital administration of FL (PHL) allows for earlier treatment and better survival rates (3). Whereas primary PCI is the preferred reperfusion therapy, PHL may be superior to primary PCI in reducing mortality among patients with ST-segment elevation myocardial infarction (STEMI) who present early (i.e., less than 2 h after the onset of symptoms) (4,5). For rural populations, PHL may be the only reperfusion strategy that can be provided in a timely manner (6).

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PHL requires a complex pre-hospital system of care to enable prompt and accurate recognition of STEMI and skilled management of life-threatening complications of PHL such as arrhythmia, major bleeding, and stroke (6). Despite this complexity, PHL has been endorsed by the European Society of Cardiology (7–9) and has been well established in Europe for over 2 decades (7–9). In contrast, PHL is available in very few American and Canadian regions (10), despite the larger territories and high proportion of rural populations in these countries compared with Europe (10–12).

Abbreviations and Acronyms

ECG = electrocardiogram
FL = fibrinolytic therapy
PCI = percutaneous coronary intervention
PHL = pre-hospital fibrinolysis
RCT = randomized controlled trial
STEMI = ST-segment elevation myocardial infarction

Insights on the infrastructures and processes that support PHL care in Europe and North America may assist other jurisdictions to implement PHL systems of care. Based on the longer European experience, patients who received PHL in these regions would be likely to have more favorable survival rates and fewer major complications than would patients treated by less-experienced PHL programs. Therefore, European PHL survival data may serve as an optimal benchmark for other PHL programs. The primary objective of this article was to describe the infrastructures and processes of selected European and North American PHL programs. The secondary objective was to report outcome data of the PHL programs surveyed.

Methods

Selection of PHL programs. We contacted cardiology experts in STEMI treatment to inquire about available PHL programs in Europe and North America. We obtained 100% response from the leading investigators of the 7 PHL programs contacted: England/Wales, France, Vienna, and Sweden from Europe; Edmonton and Nova Scotia from Canada; and Houston, Texas, from the United States.

Affiliated PHL research programs/national registries. All the participating PHL programs had affiliated research projects which were MINAP (Myocardial Ischemia National Audit Project) in England/Wales (13), FAST-MI (French Registry on Acute ST-Elevation Myocardial Infarction) in France (14), RIKS-HIA (Register of Information and Knowledge About Swedish Heart Intensive Care Admissions) in Sweden, Vienna-STEMI Registry in Vienna, AMICO (Alliance for Myocardial Infarction Care Optimization) in Houston, Vital Heart Response in Edmonton, and the Cardiovascular Health Nova Scotia Program in Nova Scotia.

Data collection. PHL may have different impacts on STEMI morbidity and mortality depending on the rural-urban mix of the population served and access to hospitals that can deliver alternate reperfusion therapy such as primary PCI. Most recent data relevant to each PHL program included in this study on the territory and population served were extracted from the official Website of United Nation Statistics (available only for the year 2008) (15). We defined "rural" as all "nonurban" regions with a population of less than 1,000 persons, and a population density less than 400 persons per km^2 (Organisation for Economic Co-operation and Development's definition) (16). For jurisdictions other than countries, we extracted population and geography data

Memorial Hermann Heart and Vascular Institute, Houston, Texas; and the †††Division of Coronary Artery Disease and Intensive Cardiac Care, Hôpital Européen Georges Pompidou, Paris, France. The MINAP (Myocardial Ischemia National Audit Project) and Cardiovascular Health Nova Scotia were funded mainly by government health agencies. The AMICO, RIKS-HIA, and Vienna STEMI Registry received partial support from pharmaceutical companies, and the Vienna STEMI Registry was partially supported by the Association for the Promotion of Research in Arteriosclerosis, Thrombosis, and Vascular Biology. The Unités des Soins Intensives Coronariens 2000 registry was funded by Aventis. The FAST-MI is a registry of the French Society of Cardiology, funded by unrestricted grants from Pfizer and Servier, and by an additional grant from the Caisse Nationale d'assurance-maladie (National Health Insurance system). Dr. Huynh has received minor grants for organization of educational symposia from RocheCanada in 2009 and 2010. Dr. O'Loughlin holds a Canada Research Chair in the Early Determinants of Adult Chronic Disease. Dr. Stenestrand was the President of the RIKS-HIA Registry. Dr. Schull holds a Canadian Institutes of Health Research Applied Chair in Health Services and Policy Research. Dr. Welsh has received research grants from Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis, Eli Lilly, Portola, Abbott, and Medtronic; and he was on the advisory boards for and received honorarium from AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, Roche, and Eli Lilly. Dr. Tu is supported by a Tier 1 Canada Research Chair in Health Services Research and a career investigator award from the Heart and Stroke Foundation of Ontario. Dr. Danchin has received lecturing/consulting fees from AstraZeneca, Eli Lilly, Novo, Sanofi-Aventis and Servier; lecture fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Menarini, Merck-Serono, MSD-Schering-Plough, Servier, and Sanofi-Aventis; and grant support from AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck-Schering-Plough, Novartis, Pfizer, Sanofi-Aventis, Servier and The Medicines Company. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Dr. Ulf Stenestrand is deceased.

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Table 1. Characteristics of Countries, Provinces, and Cities With PHL Programs in 2010

	Country			Province	City		
	England/Wales	Sweden	France (Excluding Territories and Corsica)	Nova Scotia (Canada)	Houston, Texas*	Edmonton, Alberta (Canada)	Vienna (Austria)
Total population (million) served by the PHL program	54.5	9.0	61.0	0.9	2.1	1.2	1.7
Area (km^2) served by PHL program	151,174	441,370	551,500	55,491	1,499	9,532	414
Population density, mean no. persons/km^2	360	21	112	16	1,400	126	4,589
Rural population, % of total population	20	15	17	45	NA	15	5
No. STEMI/year	27,000	6,000	35,000	NA	211	780	1,200
No. STEMI/100,000 population	50	66	55	NA	10	65	70
No. hospitals that provide STEMI care	224	74	223	8	30	5	6
No. hospitals with PCI facility (% of hospitals that provide STEMI care)	98 (44)	29 (39)	127 (57)	1 (12.5)	22 (73)	2 (40)	6 (100)
Population per hospital with PCI facility	556,122	310,344	480,315	900,000	175,000	600,000	316,666

*Data from Houston include surrounding areas and exclude STEMI patients who presented directly to hospitals without using pre-hospital transportation services.
NA = not available; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

in 2008, from the national statistical Websites that is, for England and Wales (Office for National Statistics of England) (17), for Nova Scotia and Edmonton (Statistics Canada) (18), for Vienna (City of Vienna Information Center) (19), and Houston (United States Census Bureau) (20). Data on the number of hospitals, the proportion of hospitals with PCI facilities (PCI-hospital), and the annual incidence of STEMI within each jurisdiction were provided by the leading investigators of the PHL programs surveyed.

In August 2008, we mailed a self-administered questionnaire (Online Appendix 1) to the lead investigators of 7 participating PHL programs. The questionnaire collected data on pre-hospital services available, as well as information on the infrastructure of the PHL program and how the program worked (i.e., its processes). Questionnaires were completed in full by all the surveyed programs in April 2009. We recontacted respondents in June 2010 to inquire about recent modifications to the PHL programs.

The investigators were also asked to report the aggregate data since the initiation of the PHL program, as well as for the years 2005 to 2008. Outcomes data in these recent three years would be more clinically relevant than outcome data in the past decade because there were numerous recent innovations in the treatment of STEMI. Due to confidentiality issues, we could not obtain individual patient data from the PHL programs surveyed.

Results

There was marked variation in the proportion of the population living in rural areas and the mean population density in the areas surveyed (Table 1). The mean population density varied from 16 persons/km^2 in Nova Scotia to 4,189 persons/km^2 in Vienna. The proportion of the population living in rural areas varied from 5% in Vienna to 45% in Nova Scotia. Access to PCI-hospital was also limited in

Table 2. Interpretation and Transmission of Pre-Hospital ECG in 2010

	Country			Province	City		
	England and Wales	Sweden	France (Excluding Territories and Corsica)	Edmonton, Alberta (Canada)	Houston, Texas	Nova Scotia (Canada)	Vienna (Austria)
Year pre-hospital ECG became available	2000	1990	1990	2002	2005	2006	2000
% of ambulance personnel trained to interpret ECG	100	100	100	100	100	32	100
Electronic transmission of ECG, % of pre-hospital ECG	Not routinely done	100	0	100	100	100	Pilot
Failed electronic transmission of pre-hospital ECG	Nonapplicable	≤1%	Nonapplicable	5	20	10	Nonapplicable

ECG = electrocardiogram.

Table 3. Expertise of the Personnel Responsible for Pre-Hospital STEMI Care (in the Ambulance or by Telephone Assistance) in 2010

	Country			Province	City		
	England and Wales	Sweden	France (Excluding Territories and Corsica)	Nova Scotia (Canada)	Houston, Texas	Edmonton, Alberta (Canada)	Vienna (Austria)
Presence of medical doctors in the ambulances, % of ambulances	0	0	100	0	0	0	95
Advanced care paramedics* in the ambulances, % of ambulances	100	100	100	51	100	100	5
Professionals who provide telephonic guidance for STEMI management	ER physicians or CCU nurses	ER or CCU physicians	Not applicable	ER physicians	ER physicians	ER physicians and cardiologists	ER physicians and cardiologists

*Advanced care paramedics are paramedics who can provide advanced cardiac life support independently.
CCU = coronary care unit; ER = emergency room affiliated to the pre-hospital services; STEMI = ST-segment elevation myocardial infarction.

Nova Scotia with only 1 PCI-hospital in this Canadian province (ratio of 900,000 persons/PCI-hospital compared with 175,000 persons/PCI-hospital in Houston, Texas).

In most surveyed countries except for Sweden, pre-hospital ECG were available only since the year 2000 (Table 2). Most ambulance personnel were trained to interpret ECG. In Vienna and France, 95% and 100%, respectively, of ambulances were staffed with physicians (Table 3), all other PHL programs surveyed had paramedics and nurses (Sweden) able to provide advanced cardiac life support (i.e., advanced care paramedics). The PHL programs in London, Vienna, Houston, Edmonton, Sweden, and Halifax had integrated regional networks to facilitate direct transfer of patients for primary PCI (Table 4). In Vienna and Sweden, all STEMI patients were transported directly to a PCI-hospital for primary PCI, except for patients who lived in very remote rural areas in Sweden. In England/Wales, at the time of this survey, there was no formal transportation arrangement for primary PCI outside London. In the greater London area, all STEMI patients were transported directly for primary PCI. In Nova Scotia, direct transfer for primary PCI was only possible for patients with STEMI living in Halifax.

Except for England/Wales, where paramedics could independently initiate PHL, PHL could only be administered after transmission of pre-hospital electrocardiogram (ECG) and authorization from responsible physicians in the other PHL programs (Table 4). In Houston, Nova Scotia, and Edmonton, PHL was administered by paramedics; in Sweden, by ambulance nurses; and in France and Vienna, PHL was administered by physicians in the ambulances.

We described the characteristics and outcomes of patients who received PHL in Tables 5 and 6. Reinfarction was uncommon with cumulative incidences that ranged from 2.4%

Table 4. Pre-Hospital Care of Patients With STEMI in 2010

	Country			Province	City		
	England and Wales	Sweden	France (Excluding Territories and Corsica)	Nova Scotia (Canada)	Houston, Texas	Edmonton, Alberta (Canada)	Vienna (Austria)
Routine transfer of patients for primary PCI, % of STEMI patients	100 for London, no routine transfer for primary PCI outside London	87	NA	Only in Halifax	85	60	100*
Responsible to authorize PHL	Paramedics	ER physicians	Physicians in the ambulances	Physicians affiliated with the pre-hospital services	ER physician	Physicians affiliated with the pre-hospital services	Physicians in the ambulances
Types of fibrinolytic therapy, % of patients who received PHL	TPA: 0.15, Reteplase: 19.9, TNK: 79.5	(1995–2008) SK: 4, TPA: 11, Reteplase: 62, TNK: 24 since 2004 only reteplase and TNK were used	TNK: 100	TPA: 11, Reteplase: 4.2, TNK: 82.2, undetermined: 3.2	Reteplase: 100	TNK: 100	TNK: 100
Routine angiography after PHL, % of patients who received PHL	75	50	85	100% in only Halifax	100	90	90

PHL = pre-hospital fibrinolysis, SK = streptokinase; TNK = tenecteplase; TPA = tissue plasminogen activator; other abbreviations as in Tables 1 and 3.

Table 5. Characteristics of Patients Who Received PHL Therapy

	England and Wales 2003–2008	France 2000	France 2005	Edmonton, Alberta 2000–2002	Vienna 2003–2008	Vienna 2005–2008	Sweden 1995–2008	Sweden 2005–2008
n	12,888	180	331	119	350	191	6,643	883
Mean age, yrs	62.1 ± 11.6	59.4 ± 12.9	60.5 ± 12.5	61.3	58 ± 12	57 ± 12	66.4 ± 11.4	66.7 ± 11.3
Women, %	21.8	16.0	20.5	24.4	26.6	28.6	28.0	27.0
Mean systolic blood pressure, mm Hg	133 ± 25	127 ± 23	130 ± 25	120	129 ± 27	132 ± 27	135.5 ± 27.6	135.9 ± 27.6
Prior myocardial infarction, %	11	10	9	17.1	12	12	17	13
Prior PCI, %	13	7	7	NA	5	5	5	6
Prior CABG, %	2	2	2	NA	1	0.5	3	2
Prior CVA, %	2	1	1	NA	NA	NA	4	5

Values are n, mean ± SD, or %.
CABG = coronary artery bypass graft; CVA = cerebrovascular accident; other abbreviations as in Tables 1 and 4.

(France) to 5.8% (England/Wales). Less than 2% of PHL patients (≤0.6% in most programs) experienced in-hospital stroke. The French PHL program had the lowest mortality at 2.7% in-hospital and 4.5% at 1 year, whereas Sweden had the highest in-hospital mortality at 6.5% and 10.7% at 1 year.

Discussion

Although the efficacy and safety of PHL were demonstrated in several randomized clinical trials (RCTs) (2–5), the generalizability of these results is limited by differences in characteristics of patients and systems of care in the "real-life" context. Real-life patients are often older and sicker with more comorbidities than patients enrolled in RCTs (21). Because of their generally larger samples sizes and longer follow-up durations than RCTs (22,23), data from cohort studies, such as those reported in this article, may offer invaluable insights into the real-life effectiveness of PHL.

There are several barriers to PHL implantation in North America (24). First, the cost of a PHL program may be prohibitive for many pre-hospital agencies (24). Furthermore, emergency physicians may be reluctant to authorize PHL for patients whom they have not yet evaluated for fear of litigation. There may also be misperception that PHL is not necessary considering that 79% of Americans and 59% of Canadians live within an hour of a PCI-hospital (13,26) and therefore should be able to undergo primary PCI in a timely manner. However, the preceding estimate was based purely on geographic distance and without consideration of bad weather and traffic congestion. Despite the large number of PCI-hospitals and shorter distances to PCI-hospitals in Europe, PHL remains a valuable reperfusion strategy endorsed by the European Society of Cardiology (7–9).

Pre-hospital ECG is an essential prerequisite for PHL and endorsed by the American Heart Association and American College of Cardiology (2). However, only a minority of North American pre-hospital medical services can perform ECGs in the ambulances (10,11). Transmission problems might have further prevented implementation of pre-hospital ECG in many regions. Among the PHL programs surveyed, ECG interpretation in the ambulances can either be automated (i.e., interpreted by a computer) or undertaken by paramedics or by nurses. Although ECG transmission could be helpful for patients with unclear diagnoses, well-trained paramedics and nurses could diagnose and treat most STEMI successfully without ECG transmission.

The outcomes reported in this article provided important insights into the effectiveness and safety of PHL within several different contexts and time spans. These results were similar to the outcomes reported by other American PHL programs (26). Denktas et al. (26) reported similarly low

Table 6. Major Adverse Events in Patients Who Received PHL Therapy

	England/Wales 2003–2008	France 2000	France 2005	Edmonton, Alberta 2000–2002	Vienna 2003–2008	Vienna 2005–2008	Sweden 995–2008	Sweden 2005–2008
Major bleed, %	0.9*	NA	1.2	10.9	3.7	3.1	2.4	3.5
Reinfarction, %	5.2†	2.8	2.4	5.0	5.4	5.2	2.9	1.5
Stroke, %	0.5‡	1.1	0.6	1.7	1.4	1.6	0.6	0.8
In-hospital mortality, %	3.3§	3.3	2.7	3.4	6.5	4.7	6.5	5.7
1-yr mortality, %	6.9‖	5.6	4.5	NA	NA	NA	10.9	10.4

*Data available for 11,170 patients. †Reinfarction was ascertained only since 2005. ‡Data available for 11,310 patients. §Data available for 5,941 patients (2007–2008). ‖Data available for 5,721 patients (2007–2008).
NA = not available.

incidences of major adverse outcomes (mortality of 3.8%, stroke of 1.8%, and reinfarction of 0.8%). The higher in-hospital and 1-year mortality in patients who received PHL in Sweden, relative to PHL in other jurisdictions may be partially explained by a 5-year difference in mean age. Overall, the relatively low incidences of major adverse outcomes following PHL suggested that this reperfusion strategy could be administered safely and effectively by healthcare professionals of diverse trainings and expertise.

PHL should not be viewed as an alternate option, but rather as a complementary reperfusion strategy to primary PCI for patients with STEMI. An ideal PHL program would incorporate formal protocols that identify patients who would benefit from direct transport for primary PCI where appropriate and those who would benefit from very early FL. This would need to take account of *who* the patient is (i.e., patient characteristics), *where* the patient is (i.e., distance from a PCI-hospital), *what* is available for treatment, and *how soon* the patient presents after onset of symptoms. In this way, tailored reperfusion therapy would be provided for each STEMI patient depending on his or her circumstances.

In addition to facilitating transfer, integrated regional networks of PCI-hospitals can be invaluable for continuing cardiac care following PHL. After PHL, patients can be transferred to PCI-hospitals and then triaged for selective nonurgent PCI for patients with successful coronary flow restoration with PHL or rescue PCI for patients who did not have unsuccessful PHL. By expediting coronary reperfusion, PHL can prevent undue time delays with the associated increased risks of mortality and irreversible myocardial damage. In addition, PHL may reduce the economic burden of STEMI by decreasing the need for urgent PCI outside regular working hours.

Study limitations. First, comparison of morbidity and mortality data across PHL programs could not be undertaken due to the lack of individual patient data. Second, our description of structures and processes of the PHL programs relied on a self-administered survey by the different administrators. Although we did query some inconsistencies and cross-check with other sources of information (27) and other experts in reperfusion therapy, we did not systematically validate all responses provided by the investigators. Third, our survey did not incorporate economic and quality assurance aspects (e.g., paying process of the fibrinolytic drugs, training and monitoring of outcomes). Finally, the outcome data were derived from observational studies and therefore were subject to all the biases inherent to this type of study such as selection, confounding, and information biases. Despite these limitations, we believe that the outcome data of PHL, as reported in this manuscript, provide valuable information and may serve as benchmark for other programs of reperfusion therapy.

Conclusions

PHL has been successfully deployed in a wide range of geographic territories with varying population densities; access to PCI-hospitals and annual incidences of STEMI. PHL systems comprise a variety of different processes that could be adapted to local contexts. PHL can be safely delivered by healthcare professionals with different levels of training and expertise in a wide variety of settings. Even in areas with rapid access to primary PCI, PHL remains a valuable reperfusion strategy, for patients with expected prolonged time delay from first medical contact to coronary flow restoration by primary PCI.

Combining PHL with formal protocols for direct transportation of patients to a PCI-hospital for primary PCI would allow tailored reperfusion therapy for patients with STEMI. Insights from a variety of international settings may promote widespread use of PHL and increase timely coronary reperfusion worldwide.

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The authors wish to dedicate this article to the memory of Dr. Ulf Stenestrand who coauthored this article. He inspired us with his passion and commitment to improve global cardiovascular health. May his memory continue to live.

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Key Words: acute myocardial infarction ■ electrocardiogram ■ fibrinolysis ■ percutaneous coronary intervention.

APPENDIX

To see the questionnaires, please see the online version of this article.

The Pre-Hospital Fibrinolysis Experience in Europe and North America and Implications for Wider Dissemination

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