

REVIEW ARTICLE

DEFINITION OF THE TARGET POPULATION FOR EXTERNAL PACEMAKER AS A KEY ASPECT IN SUCCESSFUL MEDICAL DEVICE HTA PROCESS

Jan Honegr¹✉, Daniel Jun¹, Kamil Kuca², Petra Maresova²

¹ Biomedical Research Centre, University Hospital Hradec Kralove, Sokolska 581, 500 12 Hradec Kralove, Czech Republic

² Faculty of Informatics and Management, University of Hradec Kralove, Rokitanskeho 62, 500 03 Hradec Kralove, Czech Republic

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Summary

In this paper we have compiled and summarized the steps which manufacturers and clinical investigators need to undertake to perform a target population definition during the Health technology assessment process of medical device, namely external cardio stimulator (pacemaker). Based on available data using top-down approach we have defined target population for external cardiostimulator and estimated, that the size of the target population for external pacing will not exceed 16000 patients per year in the Czech Republic and is of comparable size with other states in the region.

Key words: HTA; Medical Devices; target population; external pacemaker; policymaking

Abbreviations and symbols:

ACC/AHA/HRS	American College of Cardiology/American Heart Association/Hearth Rhythm Society
AV	Atrio-Ventricular
AVG	Average value
EHRA	European Heart Rhythm Association
EU	European Union
HTA	Health technology assessment
ICD	Implantable cardioverter-defibrillator
ICD-11	International classification of diseases 11th revision
MDR	Medical Device Regulation (EU 2017/745)
US	United States
UZIS	Institute of Health Information and Statistics of the Czech Republic

Introduction

In the last millennium if medical device manufacturer wanted to put a medical device in the market, he only had to show that the medical device is reasonably safe and fit for its intended purpose. Those times are gone now.

✉ University Hospital Hradec Kralove, Biomedical Research Centre, Sokolska 581, 500 12 Hradec Kralove, Czech Republic
jan.honegr@fnhk.cz

Good clinical evidence is a key aspect both in the process of market access authorization in the United States of America or conformity assessment in the European Union, but more importantly, because money only comes first, it is the crucial aspect in the process of reimbursement negotiation (1). With regard to the public finances we could generally assume that there is never enough money for all possible emerging treatments options and thus governments and other public spenders had invented methods for evaluation of impact of one course of action on the whole system. In the field of medicine, this process is called health technology assessment.

In an attempt to put new medical device on the market, manufacturers have to provide authorities or notified bodies with sufficient clinical evidence that support their claims about safety and effectiveness of their medical devices. The best option for obtaining good clinical evidence is randomized clinical trial. Pressure on the good clinical data is even more pronounced now, after the new European Medical device regulation (MDR - EU 2017/745) will come into the force in May 2020. After the date of application of MDR, the newly certified medical devices no longer could be certified without proper clinical data demonstrating safety and effectiveness of medical device. This may put great pressure on the manufacturers of legacy medical devices, whose clinical evidence depends more or less on the grandfathering of their device- i.e. long term utilization and good clinical outcomes (2-4). For our paper we have chosen the external cardio stimulator from Czech Company Mediatrade. In the case the external cardio stimulator (pacemaker) the precise definition of target population is crucial, because of the risk, that inclusion of patients, which do not benefit from the proposed interventions, may render to the conclusion that the intervention is inferior, or not cost effective comparing to other standard interventions.

Health Technology Assessment

The first attempts to reduce spending or more precisely, to allocate sources in the best possible way had emerged in 1970s in the United States according to Banta and Jonsson (5). In 1976 the US Office of technology assessment published its first study on the subject of evaluation of medical technology. According to definition of the United Nations Manual on Health technology assessment (HTA) of Medical Devices the HTA is defined as:

HTA is “the systematic evaluation of properties, effects, and/or impacts of health-care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policy-making in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods” (6).

The Health and economic evaluation is a complex endeavor which tries to find objectively justified parameters that could be expressed as the value of medical technologies. Value could be described as systematically sound and comprehensive expression of the benefits of medical technology in relation to the costs incurred in connection with this technology in a defined time horizon from the perspective of the chosen perspective (7).

Target population definition.

One of the key concepts in HTA assessment is the concept of the target population. The precise definition of target population is crucial both during the clinical investigation and also during the reimbursement negotiation, because only properly focused clinical investigation could lead to preferable outcomes, and only medical devices with well documented clinical outcomes, superior to current state of the art technology could hope to be reimbursed and thus be commercially successful. This means that medical devices manufacturers should have their target population in mental picture all the time from the first idea of a new medical device to the final stages of negotiation with public spenders about reimbursement, because only soundly defined target population gets them to their ultimate target of fully reimbursed medical device (7).

Target population is generally a group of people with a distinct health problem, which is precisely defined by several discriminants (e.g. diagnosis in terms of International classification of diseases (ICD-11) code, severity / stage of the disease, co-morbidity, age, sex, etc.) for which the technology is intended. Definition of the target population for a selected technology must be supported by verifiable sources (e.g. epidemiological literature, registers or databases, or expert judgment by clinical experts) and must take into account the actual size population (with all restrictions) that will be affected by the technology in the given time horizon (7).

Thus there are two possible approaches for the estimation of the target population. First is the top-down approach, target population size is derived using epidemiological data of the entire population, which is subsequently limited according to individual patient characteristics, based on prevalence, incidence and mortality, etc. Target population can also be calculated using the bottom-up approach, where the size of a suitable population from databases / registers is known (based on the number of patients, who have already received existing technology) (7).

Cardiac Pacing and pacemakers

Cardiac pacing is the most prominent method in the therapy of cardiac impulse generation defects. It is used in the clinical settings when one of the underlying diseases is present. Main reasons for cardiac pacing are conduction disorders that lead to important bradycardia or asystole - mainly Atrio-ventricular block (AV Block) or Sick sinus node syndrome. Important factor to consider before commitment to the pacing therapy is the state of the disease and the fact if the cause is reversible or irreversible. Detection of reversible causes is most important to prevent unnecessary long-term pacemaker therapy (8).

In past decades main approach to bradyarrhythmia classification stemmed from their etiology (e.g. sinus node syndrome, bundle branch block or myocardial infarction, while modern guidelines classifies bradyarrhythmias according to their clinical manifestation (9).

Permanent cardiac pacing

Permanent pacemakers are implanted with primary intention either to maintain desired (set as minimal acceptable) heart rate to prevent severe bradyarrhythmias or to maintain synchronous action between the left and right ventricles in the patients with heart failure (resynchronization).

Heart muscle cells (cardiomyocytes) in normal conditions respond to the electrical pacing stimulus, which induce an electrical field that is responsible for the generation of a self-propagating wave-front of action potentials. The action potential then spread from the stimulation site. The stimulation has to have sufficient difference in electrical potential and duration to initiate wave-front. Cardiomyocytes physiology otherwise prevents cells from depolarization (it is caused by minimal threshold of potential which could trigger the depolarization) or propagation of another signal (by so called "plateau" phase). If the source of the innate electro-impulses (as in sick sinus syndrome) is defective or there is an obstacle in heart conduction system, as in Atrio-ventricular block (AV block) the electric potential has to be delivered to the affected heart regions by the artificial source - the pacemaker (10).

For pacemaker to maintain steady heart stimulation, it needs to have pulse generator with stable source of energy and delivery system which is a conductor with electrode (together called lead) for transferring of the pulses to the myocardium.

Majority of available pacing systems consist of a pulse generator and one or more pacemaker leads. Leads are attached to the heart and lead tips are positioned in the target cardiac chamber. The cutting edge technology in cardiac pacing utilizes leadless pacemakers, but these are out of the scope of this article and will not be discussed further. The lead in the traditional pacemaker system serves as the conduit of electrical signals between the myocardium and pacemaker generator. Depending on the clinical needs, pacemakers offer various settings of components and programming, pacing and sensing may be accomplished in unipolar or bipolar configuration (11).

Temporary cardiac pacing by external pacemaker

As its name suggests temporary cardiac pacing is *pro tempore* solution for patients that are in the condition that would them indicated for permanent pacing, but are not yet provided with permanent pacemaker. The solution for temporary intervention is utilization of external pacemaker which could be connected either to transcutaneous or transvenous electrodes.

Inclusion criteria for patients to obtain permanent pacemaker are described below in table 1 the most common causes are - Bradyarrhythmia and AV block. Conditions for temporary pacing may arise in several types of cases.

At first it might be the situation when the main cause of bradycardia is reversible or unknown at the time of diagnosis and in this is the case when temporary solution is the preferred option. Other times when temporary pacing is needed are emergency situations arising from asystole or cardiac insufficiency symptoms. And finally temporary pacing should be method of choice during preplanned procedures of both cardiac, or general surgery if there is possible benefit for patient from pacing due to risk of bradyarrhythmia or fibrillation, when device could be used as cardioverter. The two most common types of temporary cardiac pacing are transcutaneous pacing and transvenous pacing. Of the two only the first is a noninvasive and thus is the fastest method available for critical intervention. Other not as common modes of pacing are, transoesophageal pacing and trans-pulmonary arterial pacing. The most common clinical situation in which temporary pacing is used is symptomatic bradycardia and procedures to determination if the patient needs permanent pacing (12).

Permanent Pacemaker indications.

Patients with persistent bradycardia (sinus bradycardia or AV block)	Patients with intermittent documented bradycardia (sinus bradycardia or AV block)	Patients with syncope and suspected (undocumented) bradycardia
<ul style="list-style-type: none"> • Symptoms can clearly be attributed to bradycardia due to sinus arrest or AV block. 	<ul style="list-style-type: none"> • CRT indicated when there is a documented symptomatic bradycardia due to sinus arrest or AV block. 	<ul style="list-style-type: none"> • Bundle branch block (BBB). patients with alternating BBB and in patients with BBB and positive EPS defined as HV interval of ≥ 70 ms, or second- or third-degree His-Purkinje block demonstrated during incremental atrial pacing or with pharmacological challenge.
<ul style="list-style-type: none"> • Patients with third- or second-degree type 2 AV block irrespective of symptoms. 	<ul style="list-style-type: none"> • Patients with third- or second-degree type 2 AV block irrespective of symptoms. 	<ul style="list-style-type: none"> • Bundle branch block (BBB). Pacing may be considered in selected patients with unexplained syncope and BBB.
<ul style="list-style-type: none"> • Pacing may be indicated when symptoms are likely to be due to bradycardia, even if the evidence is not conclusive. 	<ul style="list-style-type: none"> • Reflex asystolic syncope. Pacing should be considered in patients ≥ 40 years with recurrent, unpredictable reflex syncope and documented symptomatic pause/s due to sinus arrest or AV block or the combination of the two. 	<ul style="list-style-type: none"> • Carotid sinus syncope. Pacing is indicated in patients with dominant cardio inhibitory carotid sinus syndrome and recurrent unpredictable syncope.
		<ul style="list-style-type: none"> • Tilt-induced cardio inhibitory syncope. CRT may be indicated in patients with tilt-induced cardio inhibitory response with recurrent frequent unpredictable syncope and age > 40 years after alternative therapy has failed

Table 1. Indications for permanent pacing: Information in this table is adapted from *Brignole et al.* (9).

Transcutaneous pacing is option of choice in urgent situations, because of rapid initiation of pacing. Main indications are symptomatic bradyarrhythmias and as a part of advanced cardiac interventions in patients with bradycardia or asystole. During transcutaneous cardiac pacing severe side effects such as skin irritation (burning sensation) which may be combined with muscle contractions may occur. Because of this unpleasant side effects it is advisable to sedate patients, that are haemodynamically stable and conscious (9, 12).

Manufacturer of Mediatriade EPG 10P, EPG 10PM describes its indication in the end user information as obtained from Czech registry of medical devices (RZPRO) (13) as: Intermittent or complete cardiac block associated with asystole or bradycardia, sinus bradycardia. In our opinion this is very wide definition and for demonstration of safety and cost effectiveness of this device it should be defined more precisely.

Temporary pacing indications and contraindications

1. Patients with Sinus bradycardia	Patients with persistent hemodynamically unstable Sinus node disease refractory to medical therapy, temporary transvenous pacing should be applied to increase heart rate and improve symptoms until a permanent pacemaker is implanted or the bradycardia cease
	In patients with SND with severe symptoms or hemodynamic compromise, temporary transcutaneous pacing may be considered to increase heart rate and improve symptoms until a temporary transvenous or Permanent pacemaker is placed or the bradycardia cease
	In patients with Sinus node disease with minimal and/or infrequent symptoms without hemodynamic compromise, temporary transcutaneous or transvenous pacing should not be performed.
2. Patients with AV block	Patients with transient or reversible causes of AV block , such as Lyme carditis or drug toxicity , should have medical therapy and supportive care, including temporary transvenous pacing if necessary , <u>before determination of need for permanent pacing</u>
	For patients with second-degree or third-degree AV block associated with symptoms or hemodynamic compromise that is refractory to medical therapy, temporary transvenous pacing is reasonable to increase heart rate and improve symptoms
	For patients with second-degree or third-degree AV block and hemodynamic compromise <u>refractory to antibradycardic medical therapy</u> , temporary transcutaneous pacing may be considered <u>until a temporary transvenous or Permanent pacemaker</u> is placed or the bradyarrhythmia cease
3. Surgery (other than cardio-surgery)	In patients who are thought to be at high risk for the development of intraoperative or periprocedural bradycardia because of patient characteristics or procedure type, placement of transcutaneous pacing pads is reasonable
	Surgery on patient with LBBB who needs pulmonary artery catheterization for intra-operative monitoring, routine prophylactic temporary transvenous pacing should not be performed

Table 2. Indications and contraindications of temporary pacing. Informations in this table is compiled from ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay by Kusumoto et al. (14). Emphasis (bold, undreline) was inserted by authors of this manuscript.

Indication for cardiac pacing guidelines.

We have chosen to start defining target population using top-down approach. As a starting point we have chose the general population indicated for the permanent pacing as described in the European society of cardiology Cardiac Pacing and Cardiac Resynchronization Therapy Guidelines (9) and then we have applied additional criteria based on 2018 American Heart Association Guideline (14). This top-down approach enables us in this case to model the target population more precisely by exclusion of patients which will benefit neither from permanent pacing nor temporary pacing. We have made assumption that general population for temporary pacemaker interventions will be recruited from the population of patients, which are indicated for permanent pacing (criteria in Table 1) by applying inclusion and exclusion criteria for temporary pacing (Table 2). Second assumption is that there are several patients, which will benefit from temporary pacing and not necessarily needs implantation of pacemaker.

Methodology

In this paper we have chosen to use the combination of bottom up approach defining the basic population for the external cardiostimulator use in the Czech Republic as a population that underwent the type of surgery that could benefit from temporary extracorporeal pacing as reported in the Czech statistical yearbook of anaesthesiology

procedures (15) and then proceed with top down approach by which we have determined the size of potential population based on database data on the number of patients that has received implanted pacemaker as reported in the large surveys made by the World Society of Arrhythmias (16-19) and European Heart rhythm association (EHRA) (20, 21) and particularly by its Czech chapter - The Czech Heart Rhythmus Association and tune it by using exclusion criteria based on the recommendations of ACC/AHA/HRS Guideline (14) and by exclusion of patient in unsuitable risk classes as determined by American Society of Anesthesiology classification (22).

Results and Discussion

Target population size in the Czech Republic.

Current clinical practice in The Czech Republic states, based on the rule of thumb, that the target population size for external pacemaker/ cardioverter is roughly one percent of patients indicated to the resynchronization and pacing therapy.

Size of the target population of the Czech Republic for the temporary cardiac pacing could be predicted from number of patient with anesthesiology risk ASA4 (American Society of Anesthesiology Class 4 risk) as reported in UZIS yearbook (23) - in 2015 was total number of such patients 21 794. We assume, that all patients indicated for permanent pacing or cardioverter implantation and reimplantation will be included in this group according to the Doyle and Garmon (22). For the estimation of the size of this cohort we had used information periodically presented by Czech arrhythmologic society on the numbers of invasive cardiac pacemaker and cardioverter implantations. We had also collected data from publicly available sources that cover time span from 1975 to 2017 (24). Data are summarized in Fig 1. Czech arrhythmology association has participated both in quadrennial world surveys of the World Arrhythmias association in years 1997-2009 (16-19, 25) and in following initiative by EHRA since 2007 (20, 21). Number of patients with pacemakers and cardioverter is presented in Figure 1. For year 2015 the cohort size of patients scheduled for implantation of cardioverter or pacemaker will be 12 830 patients.

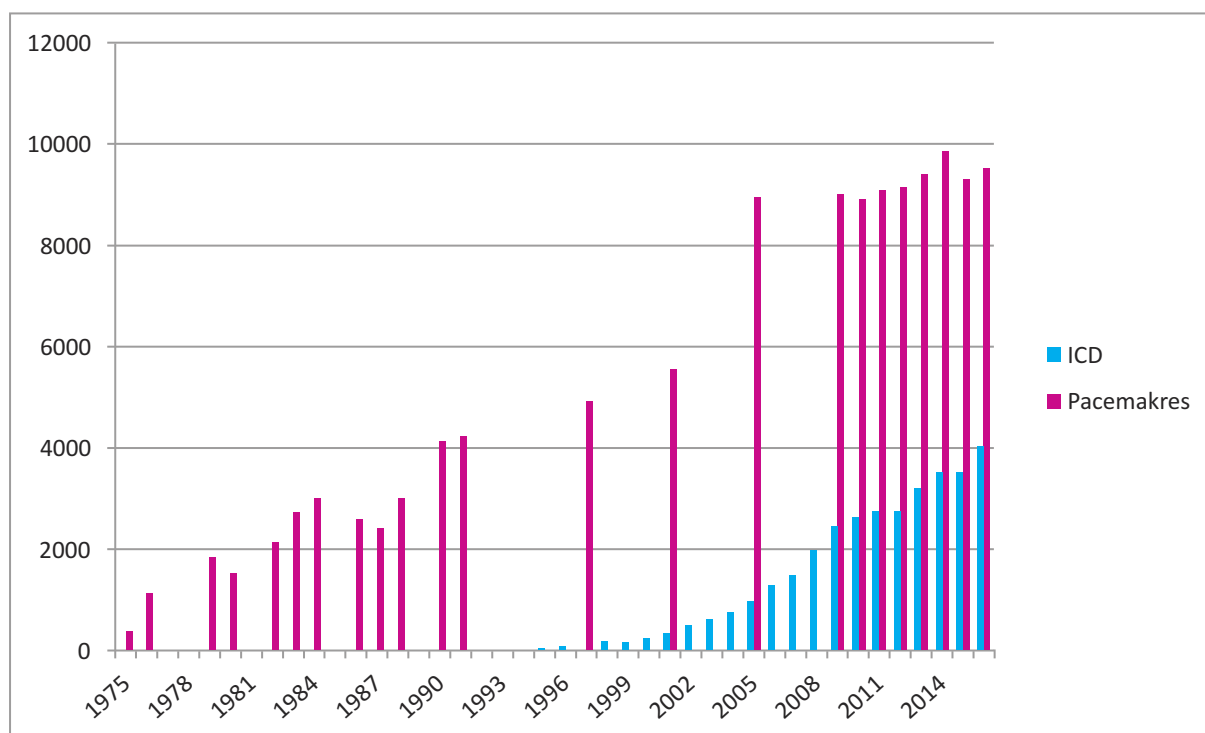


Figure 1. Historic number of implantations of pacemakers and cardioverters (ICD) in the Czech Republic. Number of implanted pacemakers is an aggregate of new implantations and reimplantations.

Table 3. Ten years change in numbers of pacemaker implantations per million inhabitants. 2007 EU28 is calculated as a number of procedures in states that in 2017 forms EU member states even if some of these states were not EU members in 2007.

	2007	2016	Change 2007-2016	2007 vs AVG 2007 EU28	2016 vs AVG 2016 EU28
Slovenia	430,8	819	190,1	54,7	92,4
Poland	495,9	786,4	158,6	62,9	88,8
Slovakia	478	693,4	145,1	60,7	78,3
Hungary	535,7	650,5	121,4	68	73,4
Germany	1201	1363,90	113,6	152,4	153,9
Estonia	720,7	799,3	110,9	91,5	90,2
Czech Republic	791,9	873,4	110,3	100,5	98,6
Ireland	423,1	462,4	109,3	53,7	52,2
Sweden	885,2	949,1	107,2	112,3	107,1
France	1000,6	1033,00	103,2	127	116,6
Austria	906,2	868,6	95,9	115	98
EU28	788	886	112,4	100	100

We presume that no more than 20% of the rest (8964 patients) of the patients from ASA4 group could benefit from the temporary pacing i.e. this cohort comprises circa 1800 patients per year.

We have summarized in Table 3 data on ten year change in pacemaker implantations from neighboring states in middle and western Europe, namely Germany, Austria, France, Slovakia, Hungary, Poland and some other EU member states to be able to compare with most developed states in EU (Germany, France) and states with similar socioeconomic conditions (Poland, Slovakia, Hungary) and with state from geographical region, with comparable level of healthcare system (Austria, Germany) (20).

Conclusions

From the presented data it could be seen, that Czech Republic is in the good position regarding cardiac pacing. The number of pacemaker implantations per million of inhabitants is roughly equivalent to the average in EU member states for last ten years, and more importantly it holds over the time. The number of procedures per million inhabitants is at level with Austria and highest from all post-soviet bloc countries. Looking onto the trend of new pacemaker and cardioverters implantations it is clear that the number of new implantations per year could raise *ceteri paribus* somewhere to region of 10 000 pacemaker procedures per year and 16 000 total pacemaker and cardioverter procedures per year. Target population size for temporary pacing in periimplantation setting in our opinion includes all patients that are indicated either for implantation, re-implantation or service maintenance of implanted pacemaker or cardioverter. Based on the recommendations of ACC/AHA/HRS Guideline (14) we presume that 20% the patients with significant risk from undercomming non heart surgery related surgical procedure could also benefit from the temporary cardiac pacing. From this presented data we estimates that size of the target population for temporary cardiac pacing in the czech republic will not exceed 18 000 patients per year.

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Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

Adherence to Ethical Standards

This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

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