Questionnaire

Hi,
You have received a research questionnaire on the topic of early evaluation of new technologies in cardiology. In the form of this questionnaire, I would like to ask you for your expert opinions on the selected issue, which is described below.
Any responses, opinions or comments obtained in this study will be anonymised.

Theoretical basis

The aim of this questionnaire is to use the method of eliciting expert opinions to obtain information about the expected effectiveness of new technology in the field of cardiology. In other words, these are methods of obtaining the opinions of experts in the form of a probability distribution, which takes place within the framework of an early assessment of health technologies (eHTA - early-stage health technology assessment).
Due to the high costs of clinical evaluation of medical devices, these costs can be prevented by early evaluation. Early-stage evaluation can serve to inform the design and development of new health technologies and procedures and to mitigate the risks associated with the practical use of new technologies and procedures.
Obtaining expert opinions within the framework of eHTA is primarily intended to supplement the unknown parameters of a new technology/treatment procedure. For this research, the evaluated technology is a new procedure in the treatment of STEMI using PCI, which, in contrast to existing procedures, would include prediction of the risk of reperfusion ventricular fibrillation (rVF) and administration of melatonin 4mg/kg before/during PCI as an antiarrhythmic in patients with a high risk of rVF.
Melatonin has been proposed for use in ischemic/ reperfusion conditions as a cardioprotective drug (Kaneko et al., 2000; Lochner et al., 2018; Sahna et al., 2005; Salie et al., 2001) and its antiarrhythmic properties have been demonstrated (Blatt et al., 1979; Diez et al., 2009, 2013; Lagneux et al., 2000; Lee et al., 2002; Tan et al., 1998; Vazan et al., 2005). Melatonin has been shown to induce a variety of electrophysiological effects in the myocardium. Specifically, it dampens the shortening of the duration of the action potential in the ischemic area (Diez et al., 2009)and increases the expression of connexin 43, thereby contributing to the improvement of conduction velocity in the ischemic myocardium (Benova et al., 2013). Both effects may be related to the antiarrhythmic action of melatonin.(Durkina et al., 2021; Sedova et al., 2019)
Specifically, the influence of Melatonin on the occurrence reperfusion (VF) has been addressed by several animal studies.
In the work of Sedova et al. (Sedova et al., 2019), melatonin was hypothesized to provide a cardioprotective effect through antioxidant properties. The association between the occurrence of ventricular tachycardia and/or ventricular fibrillation (VT/VF), oxidative stress and myocardial electrophysiological parameters in experimental ischemia/ reperfusion under melatonin treatment was evaluated. Melatonin was administered to 28 rats (10 mg/kg/day, orally, for 7 days) and 13 animals were administered a placebo. The melatonin group showed a lower incidence of VT/VF compared to the control group (29%, versus 69 %,; $p = 0.020$). Melatonin treatment was also associated with shorter baseline activation times (AT). In vitro, melatonin led to a more complete recovery of action potential duration and resting membrane potentials upon reoxygenation ($p< 0.05$). Thus, the antioxidant properties of melatonin were associated with its effect on the duration of repolarization, while the antiarrhythmic effect associated with melatonin was associated , according to the authors, with its effect on ventricular activation independent of oxidative stress.(Sedova et al., 2019)
In a study by Tan et al. (Tan et al., 1998) the authors hypothesized that cardiac arrhythmias during ischemia/reperfusion are related to free radicals generated in the heart, especially during the reperfusion period. The percentage of cases that developed ventricular fibrillation (VF) during reperfusion was recorded at the table 1.(Tan et al., 1998)

Tab. 1: The percentage of cases that developed ventricular fibrillation (VF) during reperfusion. (Tan et al., 1998)

Group	Period infusion	Number probands (n)	VF incidence rate during reperfusion (%)
Controlling	-	10	90
Melatonin 1 μM	ischemia and reperfusion	10	50
Melatonin 10 μM		10	20
Melatonin 50 μM		10	30
Melatonin 10 μM	reperfusion	10	40

The authors concluded that the low toxicity of melatonin may bring closer the perspective of its use in individuals with ischemic heart disease and arrhythmias. They also consider it appropriate to test melatonin in clinical trials

for the prevention of possible ischemia/ reperfusion -induced arrhythmias during bypass surgery, vascular spasms of the coronary arteries, or patients with thrombolytic disease. (Tan et al., 1998)
A study by Diez et al. (Diez et al., 2009) reported that reperfusion after a short period of cardiac ischemia triggers ventricular arrhythmias attributable to ion imbalance and oxidative stress. Melatonin reduced the incidence of reperfusion arrhythmias from 100% in the control group (n=11) to 50% in the 5 μM (n=10) and 10 μM (n=10) groups, to 40% in the 20 μM (n=10) and 30 % at 50 μM (n=10). (Diez et al., 2009)
A study by Diez et al. (Diez et al., 2013) it is based on the fact that although melatonin has been proven to reduce the incidence of reperfusion arrhythmias when administered before coronary occlusion, but in the clinical context of acute coronary syndromes, most therapies are administered only at the time of reperfusion. At the same time, patients often have physiological differences that can reduce the response to therapeutic interventions. Melatonin administration (50 μM) initiated at reperfusion after 15 minutes of regional ischemia reduced the incidence of ventricular fibrillation from 83% to 33% in the Wistar strain Kyoto (WKY), from 92% to 25% in fructose-fed rats (FFR) and from 100% to 33% in spontaneously hypertensive rats (SHR). The authors thus concluded that melatonin protects against ventricular fibrillation when administered during reperfusion, and these effects are preserved in rat hearts exposed to major cardiovascular risk factors. These results, according to the authors, support the continued transfer of this substance into clinical trials. (Diez et al., 2013)
In the studies, melatonin demonstrated antiarrhythmic properties under ischemic/ reperfusion conditions and consistently prevented the development of reperfusion VT/VF in rodents in vivo or on isolated heart preparations.

Description of elicitation
Information and statistical data on clinical trials or STEMI patient studies about effectiveness of using melatonin for rVF prevention have not yet been published, which is common for new developing technologies in healthcare. And that is why the eHTA concept takes into account such a situation and there is the possibility of using the elicitation of experts.
To determine the expected amount of medicine administered to human patients, a form of brain storming was chosen with the participation of one of the research groups, which deals with the effect of melatonin on reducing the risk of reperfusion VF. In conclusion, it was assumed that human patients with STEMI indicated for PCI would be administered melatonin in the amount of 4 mg/kg before reperfusion. In addition to physiological parameters and information on the effects of melatonin on human patients, a study on pigs was taken into account (Bernikova et al., 2022), where an identical dose was used. rVF occurred in 9 cases out of 13 pigs in the control group and in 4 cases out of 12 pigs in the melatonin group. (Bernikova et al., 2022)
We ask you, as experts, to supplement your idea of the values of selected unknown parameters of the new technology based on your practical and professional knowledge and experience with conventional methods of therapy for patients with STEMI undergoing PCI.
The questions invite you to fill in a numerical value or choose a specific answer variant. Furthermore, there is a space for a comment for each of the questions, but it is up to you whether you want to leave it.

Questions about the issue

1. We have 100 patients. All have STEMI, and using a new diagnostic method, it was determined that all 100 patients will develop VF during reperfusion (PCI) if they do not receive therapy. All 100 patients will receive therapy - melatonin 4mg/kg before/during PCI. How many of them getting VF during PCI?

Please give a numerical answer, e.g. "10 "

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You can add comment here (optional)
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2. Do you consider the dosage of melatonin 4mg/kg appropriate if it is administered as an antiarrhythmic before/during PCI for STEMI patients with a high risk of reperfusion VF?
- ☐ YES
- ☐ NO (If NO, please add a comment or suggestion to change the dosage.)

You can add comment here (optional)

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3. How would you define using CTCAE v5.0 level of adverse effects of the selected dosage of melatonin 4mg/kg, assuming that it is administered before/during PCI as an antiarrhythmic for STEMI patients with the high risk of reperfusion VF?

- ☐ Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- ☐ Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. (ADL – Activities of Daily Living)
- ☐ Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- ☐ Grade 4 Life-threatening consequences; urgent intervention indicated
- ☐ Grade 5 Death.

You can add comment here (optional)

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4. Do the benefits outweigh the risks associated with the administration of melatonin 4mg/kg, assuming that it is administered before/during PCI as an antiarrhythmic for STEMI patients with a high risk of reperfusion VF?

- ☐ YES, benefits outweigh the risks
- ☐ Rather yes
- ☐ don't know
- ☐ Rather not
- ☐ NO, benefits do not outweigh the risks

You can add comment here (optional)

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Additional questions

This part of the questionnaire is focused on additional questions about this study and your opinions.

What is your overall professional experience?

- ☐ >10 years
- ☐ 5-10 years
- ☐ <5 years
- ☐ 0 years

What is your current job position?

- ☐ The head of the organization
- ☐ Deputy head
- ☐ Head of Department
- ☐ Deputy Head of Department

What is your level of education?

- ☐ Ph.D.
- ☐ M.D.
- ☐ Ing. / M.Sc.
- ☐ B.Sc.

What is your experience with the issue of reperfusion ventricular fibrillation of STEMI patients during PCI?

- ☐ >10 years
- ☐ 5-10 years
- ☐ <5 years
- ☐ 0 years

What is your level of participation in the development of technologies/procedures related to the issue of reperfusion ventricular fibrillation of STEMI patients during PCI?

- ☐ I specialize in the given issue
- ☐ I participate in practical work to solve the problem, but the issue does not fall into my stated specialization
- ☐ The issue falls within my specialization
- ☐ The issue does not fall under my specialization

At the end of this questionnaire, I would like to thank you for your time.

Here you can add a comment/rating/notes/suggestions/opportunities (optional)

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