Choosing wisely in cardiology: Five proposals from the Italian Association for Cardiovascular Prevention and Rehabilitation

Marika Werren[1], Roberto Copetti[2], Nicola Gaibazzi[3], Franco Giada[4], Andrea Faggiano[5], Chiara Ricci[6], Pompilio Faggiano[7]

[1]Cardiac Rehabilitation Unit, Institute of Physical Therapy and Rehabilitation "Gervasutta", University Hospital, Udine; [2]Emergency Medicine Unit, University Hospital of Cattinara, Trieste; [3]Cardiology Unit, Maggiore Hospital, Parma; [4]Sports Medicine Unit, Cardiac Rehabilitation, Health Unit 3 "Serenissima", Venice; [5]Medical Student, University of Milan; [6]Gastroenterology Unit, Department of Clinical and Experimental Sciences, University of Brescia; [7]Cardiology Division, Spedali Civili, University of Brescia, Italy

Abstract

We do not always accomplish what is best for our patients. Is "more procedures, more drugs" a real synonym of good and always useful medicine? Probably not. Indeed, it has been highlighted that many tests and treatments, widely used in medical practice, do not bring benefits to patients, but can be harmful. So, why do we keep performing them? Many reasons, surely one of the main is the constant fear of malpractice legal-medical consequences; this led to the development of a defensive medicine, no longer focused on the health of the patient. For this reason, the Italian Association of Cardiac Prevention and Rehabilitation (GICR-IACPR) joined an international project "Choosing Wisely", supported by the Slow Medicine Initiative, a network which states that "Less is more". The purpose of the "Choosing Wisely" project is to improve the quality and safety of health services through the reduction of practices that, according to available scientific knowledge, do not bring significant benefits to the patients, but can, on the opposite, expose them to risks. This GICR-IACPR paper proposes to avoid five widespread practices in cardiology, at risk for inappropriateness and lacking of clinical evidence of benefit: i) do not perform routine chest X-ray in patients entering rehabilitation programme after cardiac surgery; ii) do not perform Computed Tomography for coronary calcium score in patients at high cardiovascular risk; iii) do not perform Holter electrocardiographic monitoring in patients suffering from syncope, near syncope or dizziness, in whom a non-arrhythmic origin has been documented; iv) do not routinely prescribe proton pump inhibitors (PPI) for gastrointestinal bleeding prophylaxis in patient with single drug antiplatelet therapy in absence of additional risk factors; v) avoid routine use of infective endocarditis prophylaxis in mild to moderate native valve disease.

Correspondence: Dr. Marika Werren, Cardiac Rehabilitation Unit, IMFR Gervasutta, Azienda Sanitaria Universitaria Integrata di Udine, Via Gervasutta 48, 33100 Udine, Italy.
E-mail: marika.werren@asuiud.sanita.fvg.it

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Introduction

Most of the physicians worldwide believe that "more procedures, more drugs" is a marker of high-quality medical practice. However, it has been demonstrated that many tests and pharmacological or surgical treatments, widely used in medical practice, in fact do not bring benefits to patients, but can be harmful. Such examinations and treatments are typically the ones not supported by efficacy evidence, but they continue to be prescribed and carried out for multiple reasons: to meet the pressing demands of patients, in fear of legal-medical consequences if not done, for economic interest, to demonstrate a vast scientific culture or to apply, in an uncritical way, the arguable concept of "doing whatever possible for my patients". Moreover, explaining the potential pros and cons of an exam or procedure to patients and their families often requires much more time and patience than perform it right away; moreover, in some health systems the quantity of medical services is rewarded more than their quality and appropriateness.

An unnecessary examination or treatment can expose the patient to needless risks, much more than we are used to consider. Not to mention the useless additional costs for the health system. For this reason, Slow Medicine, a network of professionals and citizens who recognize themselves in simple, respectful and appropriate practice of medicine has launched in Italy the project "Less is More", belonging to the International Choosing Wisely network with the name of "Choosing Wisely Italy". The purpose of the "Choosing Wisely Italy" project is to improve the quality and safety of health services through the reduction of diagnostic tests and treatments that, according to available scientific knowledge, do not bring significant benefits to the patients, but, on the contrary, can expose them to unnecessary risks. The project, through the reduction of inappropriateness, is expected to achieve a more

appropriate and fair use of available resources with greater economic sustainability of health systems, even if the aim of the Italian project is not specifically "saving money" but "saving health".

Cardiac Prevention and Rehabilitation (CPR) is the subspecialty of clinical cardiology dedicated to the treatment of cardiac patients in both the post-acute and chronic phases. The mission of CPR has changed over time [1-2]. From being centred on the acute phase, the challenge now is to guarantee continuity and quality of care in the medium and long-term chronic phase. In this clinical setting it is mandatory to introduce the "Choosing Wisely" culture. On this ground the Italian Association of Cardiac Prevention and Rehabilitation (GICR-IACPR) joined the project in 2015, identifying five widespread practices at risk of appropriateness (Table 1). The aim of this report is to present in detail these practices.

Do not perform routine chest X-ray in patients entering rehabilitation programme after cardiac surgery

The routine use of a further X-ray examination of the thorax at entry into Cardiac Rehabilitation program, in absence of symptoms or signs at physical examination that would suggest a new complication, is completely inappropriate and possibly harmful to the patient, considering the possibility of using a non-invasive method, such as ultrasound, to assess the lung fields.

For many years, lung ultrasound has been considered almost useless for the assessment of the lungs, except for detecting pleural effusions and few other indications. In the last decade, it has been understood that the applications in the clinical field were larger and clinically useful, with the great advantage of bedside evaluation [3-9].

Lung ultrasound has some peculiarities that make it unique, since lung ultrasound assessments can be done at the bedside, repeated several times, without risk of irradiation and because it is performed with minimal or absent discomfort for the patient [3]. Furthermore, it somehow explores what theoretically cannot be studied with ultrasound: air. In fact, the lung, as any other parenchymatous organ, ca be explored by ultrasound only when the aeration inside it is absent or considerably low. With ultrasound it is possible to diagnose diseases like pneumonia, atelectasis or tumours in the periphery of the lung. When lung deaeretion is not so important as to make it a real parenchyma, the interactions of ultrasound with the periphery of the lung generate vertical artifacts, the so-called B lines (Figure 1). When the lung is normally ventilated, only horizontal artifacts, A lines, expression of reverberations of the pleural line, are evident [10].

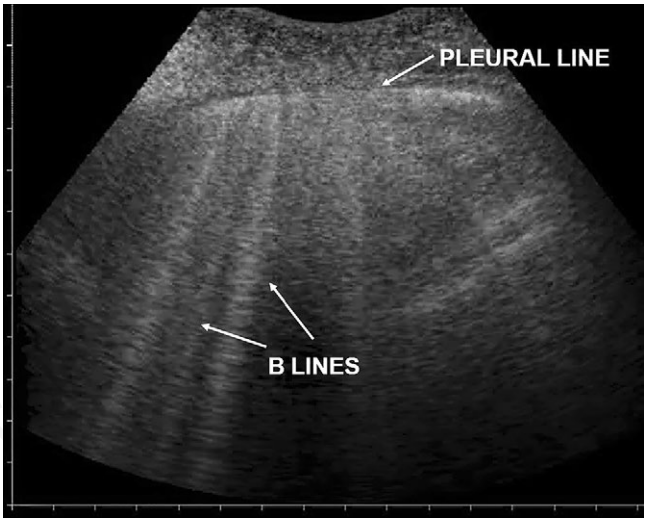

Figure 1. Lung ultrasound showing B lines indicating pulmonary congestion.

Table 1. Five recommendations from Italian Association for Cardiovascular Prevention and Rehabilitation (IACPR).

1	**Do not perform routine chest X-ray in patients entering rehabilitation programme after cardiac surgery** Patients always receive chest X-ray before discharge from cardiac surgery. Further X-ray should be warranted only on clinical basis. Pleural effusion monitoring should be performed by mean di thoracic echography
2	**Do not perform Computed Tomography for coronary calcium score in patients at high cardiovascular risk** "Coronary calcium score" is not predictive of cardiovascular events in subjects already at high risk using traditional score systems
3	**Do not perform Holter electrocardiographic monitoring in patients suffering from syncope, near syncope or dizziness, in whom a non-arrhythmic origin has been documented** Holter monitoring is indicated if the likelihood of arrhythmia causing a syncope is elevated. Monitoring devices should be chosen according to syncope frequency: Holter electrocardiographic monitoring for daily symptoms, external loop recorder for weekly, and subcutaneous implantable device for monthly or less frequents events.
4	**Do not routinely prescribe proton pump inhibitors (PPI) for gastrointestinal bleeding prophylaxis in patient with single drug antiplatelet therapy in absence of additional risk factors** Gastrointestinal (GI) bleeding risk is increased in presence of double antiplatelet treatment. Risk factors for GI bleeding are: previous GI bleeding, peptic ulcer, advanced age, NSAID or steroid drugs use, oral anticoagulant therapy. In absence of risk factors, PPI therapy is not warranted for single drug antiplatelet treatment.
5	**Avoid routine use of infective endocarditis prophylaxis in mild to moderate native valve disease** Despite of high frequency of bacteraemia associated to dental procedures, the related risk for infective endocarditis (IE) is very low, both in general population and in cardiac patients. Extensive use of prophylaxis is not supported by evidence. Prophylaxis should be restricted to high risk patients (*i.e.*, patients with worse prognosis associated to IE or at higher risk to develop an IE).

The B lines have a high sensitivity in detecting increased extravascular pulmonary water. However, their specificity is low because they can be seen in different pathological conditions (ARDS, cardiogenic pulmonary oedema, pulmonary fibrosis, inflammatory processes, *etc.*). The pathophysiological peculiarities of cardiogenic pulmonary oedema make pulmonary ultrasound not only sensitive but also extremely specific. The B lines, in this condition, tend to be bilateral, symmetrical and with a gradient that goes from the lung base to the apex, just as extravascular water is distributed according to the hydrostatic gradient. Lung ultrasound is much more accurate than chest x-ray in the diagnosis of cardiogenic pulmonary oedema, being able to detect even small increase of extravascular pulmonary water (11).

Furthermore, the evaluation of fluid in the pleural cavity has been a well-known ultrasound application for many years. With ultrasound imaging it is possible to detect small amounts of fluid that can be missed at chest x-ray [12]. Ultrasound, differently from chest x-ray, may also suggest the nature of the effusion. The transudates appear as anechogenic effusions, while the presence of blood component or exudate has a corpusculated appearance. The "honeycomb" appearance is typical of empyema. The contextualization of ultrasound images within the clinical picture is anyway key to differentiate several apparently similar images (9).

Do not perform Computed Tomography for coronary calcium score in patients at high cardiovascular risk

Among the various imaging methods (carotid intima-media thicknesses or plaques, ankle-brachial blood pressure index, pulse-wave velocity) or laboratory markers measurement (C-reactive protein, homocysteine, BNP) tested in the last decades, it is widely documented in the literature (MESA data, Rotterdam Study, *etc.*) [14-18] that the Calcium Coronary Score (CACS) is the parameter with greater reclassification capability and greatest accuracy in addition to either the Framingham Risk Score (FRS) or the AHA/ACC model of the Pooled Cohort Equation (ASCVD risk). The financial cost and the related biological risk, although minimal, recommends CACS use for cases when it may possibly translate into up or down reclassification of risk (Figure 2). In particular, the CACS can be a useful test in the reclassification of patients at high risk according to the FRS or the Pooled Cohort equation. For example, a lifelong treatment with statin in elderly male patients (>65 years) could be not indicated with a CACS = 0. Such hypothesis was confirmed by the recent BIOIMAGE study, in which the re-stratification operated by CACS of patients with a baseline ASCVD risk >7.5% was clearly demonstrated useful in reclassifying potential candidates to statin therapy as finally not eligible for such treatment. However, in the last analysis of the MESA (Multi-Ethnic Study of Atherosclerosis), where the FRS and Pooled Cohort equation were recalibrated for the specific screened population, the advantage of using CACS in the reclassification of risk remained statistically significant at the level of population but clinically "modest" in absolute terms.

If we consider the more complex risk scores, such as the European SCORE and HEART project, recommended by the recent European guidelines for cardiovascular prevention, the use of CACS is useful in patients at intermediate risk, while it is not indicated in patients at low risk and in those at high or very high risk [19].

In conclusion, although the CACS exceeds all the other imaging and laboratory markers in the ability to stratify the risk in primary prevention on top of the clinical scores, its use must be weighed and adapted to the individual, limiting its use to patients at intermediate risk, also considering the radiological risk (biological cost) to which the patient is exposed.

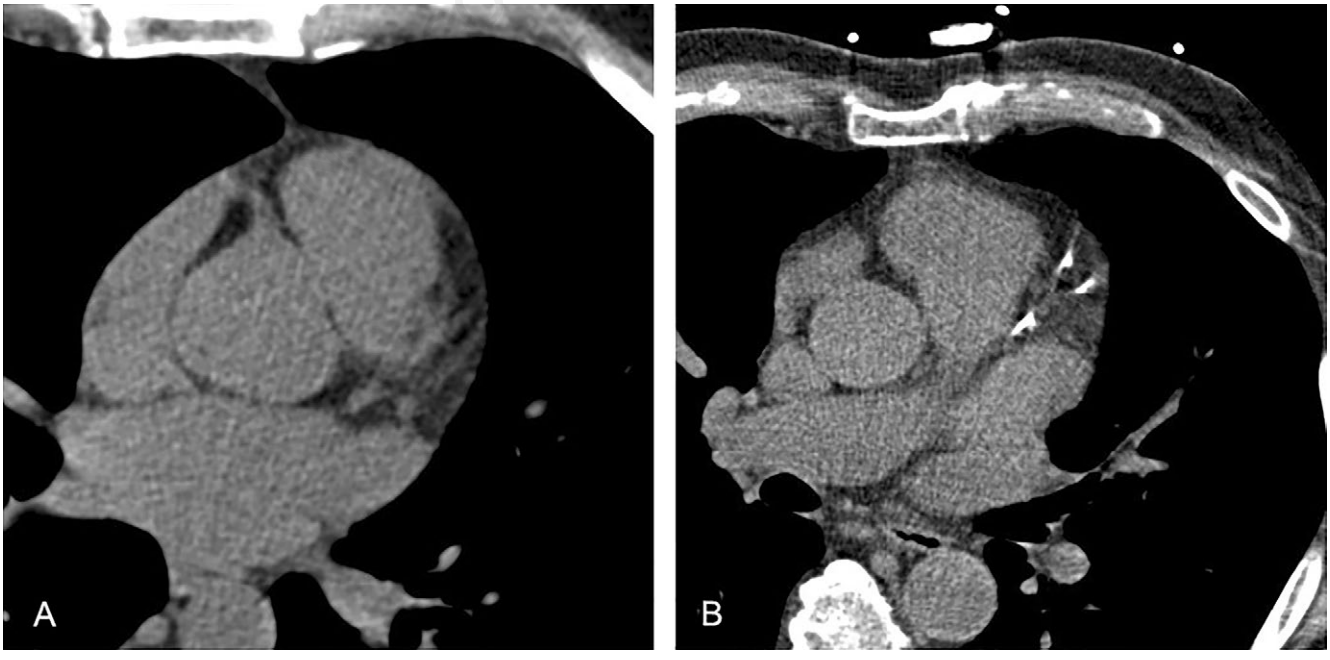

Figure 2. Computed tomography of the heart. Left: absence of calcification on the coronary tree; right: presence of diffuse calcification on the coronary arteries.

Do not perform Holter electrocardiographic monitoring in patients suffering from syncope, near syncope or dizziness, in whom a non-arrhythmic origin has been documented

The ECG-Holter is one of the currently available devices (together with external and implantable loop recorders) in the category of ambulatory ECG monitoring (AECG monitoring) devices. The AECG monitoring is used primarily to diagnose a cardiac syncope, more precisely of arrhythmic origin [20,21]. Cardiac syncope accounts for about 14% of syncope causes (3% structural cardiac causes and 11% arrhythmic causes) and is associated with a worse prognosis than syncope from other aetiologies, such as neuromediate and orthostatic ones [22]. However, unlike syncope from most other causes, there are currently effective treatments for cardiac syncope: pacemaker (PM), implantable cardiac defibrillator (ICD), ablation, cardiac surgery, *etc*. Thus, the key problem, the evaluation of patients of patients with syncope, is how to diagnose (or exclude) a cardiac cause of syncope. According to the European guidelines [20], an accurate initial assessment (including history, physical examination, resting ECG and test for orthostatic hypotension) is essential in order to differentiate true syncope from other types of transient loss of consciousness (epilepsy, vertigo, falls, *etc*.). During this thorough evaluation, in a relevant percentage of cases, it is also possible to reach a definitive etiological diagnosis of syncope, or find clues suggesting a probable cardiac cause syncope. Indeed, the presence on the ECG of severe bradycardia, sinus pauses >3 s, advanced AV block, alternation of right and left bundle branch block, sustained and rapid ventricular or supraventricular tachycardia, non-sustained polymorphic ventricular tachycardia, PM malfunction, arrhythmic storms with multiple shocks in ICD carriers, represent diagnostic elements for a cardiac (and in particular arrhythmic) cause of the syncope. On the other hand, bifascicular block, QRS duration >0.12 ms, 2nd degree AV block, non-sustained ventricular tachycardia, pathological Q waves, long or short QT, typical aspects of Brugada syndrome or arrhythmogenic dysplasia of the right ventricle represent suspicious elements for a cardiac aetiology of syncope. Moreover, also the following clinical features suggest a cardiac cause of syncope: presence of severe structural heart disease, familiar history of sudden death, advanced age, antiarrhythmic therapy, syncope without prodromes, syncope preceded by palpitations, or occurred during physical exertion or supine position.

AECG monitoring is indicated in syncope remained of unknown origin after the initial evaluation, when there is a high probability of identifying a cardiac origin of syncope and / or when there is a high probability of syncope recurrence during the monitoring period. The choice of which AECG monitoring device to use is therefore fundamental, and it depends on the frequency of syncopal spells. In case of a daily inter-syncopal interval a common ECG Holter recorder will be sufficient (which allows an AECG monitoring of 1-7 days). On the contrary, when this interval is weekly or monthly, an external loop recorder (which allows an AECG monitoring up to 4 weeks), or an implantable loop recorder (which allows an AECG monitoring up to 3 years) will be recommended, respectively [23,24]. When the common ECG Holter recorder is used too extensively, in fact, its diagnostic power is rather modest, ranging from 1% to 7%, while it increases significantly, up to 25%, if used appropriately, resulting in a significant reduction in the cost per single diagnosis and in cost saving for the health system [22].

AECG monitoring is robustly diagnostic for arrhythmic syncope (or non-arrhythmic syncope) only when it is possible to establish a correlation between syncope itself and an electrocardiographic recording. However, AECG monitoring can also be considered diagnostic in the absence of syncopal recurrence during monitoring, if sinus pauses >3 s or advanced atrioventricular blocks during daytime or sustained and rapid ventricular or supraventricular tachycardias are recorded.

Do not routinely prescribe proton pump inhibitors for gastrointestinal bleeding prophylaxis in patient with single drug antiplatelet therapy in absence of additional risk factors

Proton pump inhibitors (PPIs) are a group of "pro-drugs" that require activation in an acidic environment. The activated form covalently binds the cysteine's sulfhydryl groups (disulfide bridge) of H+ K+ ATPase, inactivating the proton pump irreversibly. In the Italian national health system, the prescription of PPI is regulated through the AIFA 1 and 48 notes. In particular, note #1 provides the use of these drugs in the case of:

– chronic treatment with non-steroidal anti-inflammatory drugs;
– antiplatelet therapy with low-dose acetylsalicylic acid (ASA).

These treatments should be supported by the presence of at least one of the following conditions:

– history of previous digestive bleeding or peptic ulcer not healed with eradication therapy;
– concomitant therapy with anticoagulants and steroids;
– age >65 years.

ASA is responsible for the damage to the gastric epithelium, due to an inhibitory effect on the production of prostaglandins, with a risk of bleeding. In particular, this risk seems to be greater in the first period after a cardio-vascular event. The incidence of gastrointestinal bleeding is estimated to be 0.48-3.64 cases per 1000 person/years in patients taking a low dose of ASA, with a relative risk of bleeding estimated to be about 1.4 (95%, CI: 1.2-1.7) [25-27].

The use of PPIs has been shown to significantly reduce the risk of bleeding of the lower gastro-intestinal tract; however, recent data have suggested their possible interference with the action of drugs such as ASA, clopidogrel and oral anticoagulants. The concomitant use of these drugs would result in a reduction of the anti-platelet effect of ASA with an increase in mortality in patients with cardiovascular disease. This effect could be related to the decreased gastric secretion with consequent alteration of the absorption and "bioavailability" of the ASA; but also to the greater co-morbidity and underlying frailty of the referred studied populations. More recently, an increase in gastrointestinal re-bleeding was confirmed in patients on ASA therapy with a previous digestive haemorrhage in a 5-year follow-up (19% users *vs* 7% non-users). Therefore, it can be concluded that the concomitant use of PPI and ASA reduces the risk of bleeding of the upper and lower gastro-intestinal tract.

The interaction between PPI and clopidogrel is linked to the metabolic activity of cytochrome 2C19. In particular, lansoprazole, omeprazole, and esomeprazole are potent inhibitors; rabeprazole and pantoprazole weak inhibitors of cytochrome 2C19. However, some studies report similar results in patients receiving clopidogrel plus omeprazole or pantoprazole, with no noticeable effects on cardiovascular mortality (patient-related variability and its ability to metabolize different drugs?). In conclusion, the data are

conflicting but, in the absence of randomized controlled clinical trial, it is recommended to use one of the weaker PPIs in high-risk patients treated with clopidogrel or in association with ASA [28].

Regarding oral anticoagulants, the combination with PPI determines an effect on their metabolism, resulting in a prolonged prothrombin time. Typically, the increased risk of bleeding occurs during the early stages of treatment, with a reported rate of bleeding of 1 to 3% person/year in randomized trials. Warfarin and PPI are both metabolized by hepatic cytochromes (CYP2C9), significantly inhibited by omeprazole. The effect of PPI on new oral anticoagulant drugs (NAO) is still controversial: a meta-analysis on 55 studies shows a greater risk of bleeding depending on the specific indications (for example post-surgery, especially orthopaedic).

Moreover, the long-term use of PPIs seems to increase the incidence of osteoporosis with greater risk of fracture in the elderly and it has been associated with micronutrients deficiencies [29] and increase in respiratory (pneumonia) and gastrointestinal infections, especially *Clostridium difficile* enteritis [30-32].

In conclusion, the use of ASA monotherapy does not require PPI except in particular high-risk categories (history of peptic ulcer, age >65 years, chronic NSAIDs or steroids), as well as therapy with anticoagulants alone does not require PPI therapy.

Therefore, the proton pump inhibitors have a high safety profile, but their long-term use must be reserved for particular conditions. Moreover, when therapy with PPIs is indicated in combination with clopidogrel in monotherapy in high-risk populations, or in combination with ASA, pantoprazole and rabeprazole should be preferred.

Avoid routine use of infective endocarditis prophylaxis in mild to moderate native valve disease

Infective endocarditis (IE) is a rare disease but with high morbidity and mortality [29,30]. For this reason, a high attention to avoid such a dangerous disease is reasonable. The concept of the prophylaxis of IE has been based on observational studies dating back to the early 1900s. The initial hypothesis assumed that the bacteraemia caused by medical procedures can cause IE, especially in patients with predisposing risk factors. For this reason, it was believed that antibiotic prophylaxis was able to prevent IE in this category of patients. The first American guidelines (1955) recommended antibiotic prophylaxis in patients with predisposing cardiac disease, although its efficacy had been demonstrated only in animal models and not in humans. These guidelines, based on expert opinions, have become standard practice used in millions of people in daily medical practice for around 50 years [31,32].

The IE is undoubtedly an ever-changing disease, characterized by changes in the microbiological profile and by an increase in the incidence of cases associated with healthcare, with elderly patients or with intracardiac devices or valve prostheses. In recent years, the epidemiological profile of the IE has undergone substantial changes, especially in industrialized countries. In the past, IE affected young adults already suffering from valvular disease (in most cases of rheumatic origin), today it mostly affects patients of advanced age who often develop IE as a result of invasive cardiac procedures or surgery.

The reduced number of indications to antibiotic prophylaxis in the last decade derives from the analysis of risk-benefit ratio [33] and from the following considerations on the pathophysiology of IE:

- low but repeated bacteraemia occurs more often during daily activities, such as teeth-brushing, use of dental floss, chewing-gum, and even more often in patients with poor dental health [34]; the virulence of low-grade bacteraemia has been demonstrated in animal models, so that the risk of human IE could be related more to low-grade cumulative bacteraemia than to sporadic short-lived peak bacteraemia after dental procedures;
- most of the case-control studies have not shown an association between invasive dental procedures and the onset of IE [35-37];
- the estimated risk of IE after a dental procedure is very low. Antibiotic prophylaxis can avoid only a small number of cases of IE (1 case of IE for 46,000 dental procedures) [38];
- the administration of antibiotic therapy is not without risk. Although not frequent, cases of anaphylactic shock may happen, sometimes deadly;
- extensive use of antibiotic therapy contributes to the big issue of microorganism's resistance to antibiotic therapy [39];
- the efficacy of antibiotic prophylaxis demonstrated on the animal model is still controversial in humans [40];
- there are no prospective, randomized, controlled trials that demonstrate the efficacy of antibiotic prophylaxis in preventing IE [41].

These considerations have led American and European cardiovascular societies to limit the prophylaxis of IE to patients at highest risk (patients with higher incidence of IE and / or patients at higher risk of unfavourable outcome in case of IE) and the UK NICE recommendations to completely contraindicate antibiotic prophylaxis in any category of patients.

The latest European guidelines (ESC 2015) [42]) recommend prophylaxis in patients at higher risk of IE (patients with valve prostheses or with valve defects corrected using prosthetic material, patients with previous IE, patients with congenital heart disease - class IIA c) who undergo high risk procedures (all procedures involving manipulation of the gingival tissue and of the periapical tooth region or perforation of the oral or respiratory mucosa).

Finally, all guidelines agree on recommending a thorough oral hygiene and periodic dental check-ups, particularly in patients at highest risk. Moreover, the adoption of most aseptic measures during the manipulation of venous catheters and during any invasive procedure is urged.

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