About cardiovascular risk in non-cardiac surgery

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The perioperative management of patients at risk for cardiovascular diseases who undergo non-cardiac surgery has been subject of debate over the past few decades and is still of great interest. An adequate perioperative management may modify postoperative mortality and morbidity and may improve the long-term prognosis. The purpose of this review is to examine the present day knowledge regarding the preoperative evaluation and perioperative and postoperative management. In spite of the available guidelines (the American College of Cardiology and the American Heart Association of 1996) and of several studies on this subject, many controversies still persist. The main questions are: 1) the preoperative cardiovascular evaluation through non-invasive tests (and the true predictive value of the increased cardiovascular risk) and 2) the real benefit of coronary revascularization before non-cardiac surgery. The last part of this review highlights many recent clinical observations and experimental studies regarding the efficacy of the extensive use of beta-adrenergic receptor blockers and optimized anti-ischemic pharmacological therapy in reducing the cardiovascular risk of non-cardiac surgery and in improving the long-term prognosis.


Key words: Beta-blockers; Cardiovascular risk; Non-cardiac surgery.

Introduction

The debate on the evaluation of the cardiovascular risk in non-cardiac surgery has been going on mainly since the 1970s, and is still subject of great interest. Over the past few decades, in fact, two elements have particularly amplified the echo of the problem:

1. the increase in the average life expectancy, and thus the increase in the number of elderly subjects who are more likely to present with concomitant cardiovascular pathologies (known or presumed) in case of surgery;
2. the improvement in surgical and anesthetic techniques which has partly reduced the risk related to the procedure itself.

Therefore, it has become necessary to carry out an accurate preoperative evaluation so as to better identify those patients who are at increased risk and, consequently, implement a perioperative management aimed at improving the prognosis particularly for this category of individuals. Over the past few years, an ever-increasing number of efforts aimed at delineating an accurate patient preoperative classification has been made in order to insert the patient into one of the various classes of risk. Some evaluation criteria, mostly complex, have been developed. These criteria considered some factors such as the patient’s medical conditions, history and known risk factors, and indicated the possible need for integrating the preoperative evaluation with instrumental investigation. Thus, the guidelines traced in 1996 by the task force created by the American College of Cardiology and the American Heart Association (ACC/AHA) first met the need of systematizing the bulk of studies carried out so far, and then tried to draw a perioperative management algorithm considering not only the patient’s risk factors and his/her clinical history, but also the type of surgery the patient was to undergo. That was also done in order to reduce the costs related to non-essential instrumental investigation and the risks deriving from unnecessary invasive procedures. Rather soon, however, these guidelines showed their limitations and contradictions. On the one hand, they extensively describe the advisability of performing procedures and provocative tests for the definition of the cardiologic risk in some groups of patients, and on the other, they do not provide any element to differentiate the clinical-therapeutic procedures, in the light of the results of the above-mentioned tests. In fact, according to the same guidelines, once the cardiovascular evaluation has been performed, the indication to myocardial revascularization is independent of the concomitant necessity for non-cardiac surgery. Moreover, there is still lack of data showing the actual protective role of revascularization through angioplasty or coronary artery bypass grafting against adverse perioperative cardiac events. Finally, according to some authors, the publication of the study of Poldermans et al.1 (although carried out on a limited sample of patients) heralded a “new era” in the perioperative management of cardiac patients; the extensive use of beta-blockers and a customized anti-ischemic therapy are indeed able to modify the incidence of early postoperative primary events and improve the long-term prognosis.
Risk classification

The first multifactorial study carried out in order to evaluate the cardiac risk in non-cardiac surgery was published by Goldman et al. in 1977. They surveyed 1001 cases and made a multivariate analysis of 39 variables, among which 8 emerged as having an independent predictive value for perioperative cardiac events; each factor was scored and a classification of the risk was obtained on the basis of the summation of the single scores. This rather complex method for assigning different classes of risk to patients did not consider important clinical variables, such as the existence and entity of anginal symptoms. In 1986, therefore, though maintaining the risk evaluation criteria substantially unchanged, Detsky et al. introduced the above-mentioned variables, thereby granting predictive value to the existence of angina (third and fourth classes according to the Canadian Society Classification). More or less in the same period (1989), Eagle et al. focused mainly on the identification of risk factors in vascular surgery, which usually presents the greatest number of complications. Even in this case, through a multivariate analysis, six clinical factors predicting adverse perioperative cardiac events have been detected: age > 70 years, history of myocardial infarction or Q wave presence on ECG, diabetes mellitus, history of angina, of cardiac failure and of a ventricular ectopic rhythm requiring therapy. However, Eagle et al. did not consider the severity of angina, nor the time elapsing since the myocardial infarction (a factor considered by Detsky et al.), nor the severity of cardiac failure. For the first time, the 1996 guidelines clearly introduced the concept of risk not from a general point of view, but with respect to the type of surgery (either emergency or elective surgery and low, medium and high-risk surgery). In 1999, Lee et al. tried to simplify Goldman’s index by proposing the evaluation of a group of patients candidate to high-risk surgery (intrathoracic, intraperitoneal and suprainguinal vascular surgery) by means of a “revised index”. They identified six independent risk factors for cardiac complications – high-risk surgery, a history of ischemic heart disease, cardiac failure, cerebrovascular pathology, preoperative treatment with insulin and preoperative creatinine serum levels > 2 mg/dL. Lee et al. observed that patients with less than two risk factors developed major perioperative cardiac events (myocardial infarction, cardiac failure, ventricular fibrillation and cardiac arrest) in less than 1% of cases, while those with two or more risk factors in 6%; they therefore demonstrated the greater utility of a classification which also considered the type of surgery, even in so far as the prognosis was concerned.

The guidelines

In 1996, the task force created by the ACC/AHA developed the guidelines on the cardiovascular evaluation of patients who were to undergo non-cardiac surgery. First, the guidelines had the merit of synthesizing the countless studies carried out so far, and secondly, they clearly highlighted the importance of the type of surgery the patient was to undergo, together with his/her clinical evaluation and the search for possible risk factors.

As far as the clinical evaluation is concerned, medical history, physical examination, and rest ECG are obviously the basic elements; a further contribution, however, may be obtained by determining the patient’s “functional capacity”, expressed in metabolic equivalent (MET) levels, i.e. the actual ability to carry out more or less intense physical activities. The Duke Activity Status Index or another standardized questionnaire are generally used; on the basis of the patient’s capacity to perform certain activities, he/she obtains a score indicating his/her functional capacity as excellent (> 7 METs), moderate (4-7 METs) or poor (< 4 METs). According to the guidelines, the operative risk is higher for patients having a poor functional capacity, irrespectively of their medical history or the type of surgery.

With regard to the clinical markers of increased perioperative risk, these are grouped into three categories (Table I).

With respect to the risk strictly related to the surgery in itself, the first consideration – in a sense taken for granted – is that emergency surgery does not allow the neces-

<table>
<thead>
<tr>
<th>Major</th>
<th>Unstable coronary syndromes (recent AMI/severe or unstable angina)</th>
<th>Congestive heart failure</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Significant arrhythmias (high-grade atrioventricular block, ventricular arrhythmias with underlying cardiopathy, supraventricular arrhythmias with an uncontrolled ventricular rate)</td>
<td>Severe valvulopathy</td>
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<td></td>
<td>Prior myocardial infarction (prior history or Q waves on the ECG)</td>
<td>Prior congestive heart failure or presently compensated heart failure</td>
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<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
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<tr>
<td></td>
<td>Mild angina pectoris</td>
<td>Uncontrolled hypertension</td>
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<td></td>
<td>Age</td>
<td>Low functional capacity</td>
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<td></td>
<td>Abnormal ECG (left bundle branch block, ST-T aspecific abnormalities)</td>
<td>History of stroke</td>
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<td></td>
<td>Rhythm other than sinus</td>
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AMI = acute myocardial infarction.
sary margin and time for a preoperative evaluation and it is anyway carried out, in spite of an increased probability of complications (not only of a cardiovascular type). It is obvious, therefore, that attention has to be focused mainly on elective surgery. The type of surgery in itself and the relevant hemodynamic stress in terms of coronary and myocardial stressogenic agents enable us to distinguish three different stages of surgical risk gravity (Table II).

Besides the above-mentioned emergency surgery, major and peripheral vascular surgery as well as surgery generally associated with significant blood loss, are therefore considered as high-risk surgery. On the other hand, intraperitoneal, intrathoracic, orthopedic and prostate surgery and carotid endarterectomy are classified as medium-risk surgery. Endoscopic maneuvers, cataract surgery and breast surgery are finally considered as low-risk surgery. According to the ACC/AHA, only by considering the type of surgery, the probability of developing perioperative complications (such as ischemic complications) is ≥ 5% in high-risk surgery, while in medium- and low-risk surgery the percentage decreases to < 5 and 1% respectively.

Thus, we have all the elements necessary to describe the guidelines’ algorithm with regard to the patient’s evaluation and the possible utility of noninvasive tests, the results of which should be decisive in order to modify the patient’s perioperative management, and sometimes could even suggest the need for further invasive investigation (coronarography) and, indirectly, revascularization.

Generally, the test, the outcome of which is able to modify the therapeutic attitude, is considered necessary. In particular, a distinction between patients with a full-blown history of heart disease and those with a negative anamnesis for cardiovascular events should be made. For the latter, in fact, it is only necessary to consider risk factors and the type of surgery they will undergo. A patient candidate for vascular surgery has a greater risk of coronary pathology, mainly because the predisposing factors (smoking and dyslipidemia) are generally the same and because possible symptoms related to the vascular disease (e.g. claudication) limit these patients’ physical performance and could conceal symptoms related to possible concomitant coronary pathology for a long time.

If the patient’s cardiac pathology is known, the stability of his/her cardiologic situation should be investigated. Obviously, if the patient suffers from an unstable coronary syndrome or one of the main predictors of cardiovascular risk (congestive heart failure, arrhythmias or severe valvular pathologies), elective non-cardiac surgery will be delayed until his/her condition is stabilized. If the patient’s condition is stable, it is necessary to distinguish patients who have been previously submitted to an invasive evaluation or even a revascularization procedure from those who just have an ascertained or presumed history of heart disease. In fact, if the patient has undergone a revascularization procedure over the last 5 years or a coronaryographic evaluation (with a favorable outcome) over the last 2 years and his/her clinical conditions remained stable, without any onset of new ischemic symptoms/signs, then further tests are generally not necessary. But, if the patient presents with intermediate predictors of risk (a history of acute myocardial infarction, past failure with present hemodynamic compensation or long-standing diabetes mellitus), a further stratification might be useful depending on his/her functional capacity and on the type of surgery he/she has to undergo. A limited functional capacity generally requires further tests especially for patients in whom high-risk surgery is indicated.

Among noninvasive tests, echocardiography and radio-isotopic ventriculography may provide a picture of the ventricular function at rest. Many studies showed a relationship between ejection fraction, especially when it is < 35%, and adverse perioperative cardiac events. However, there are no data suggesting that patients with stable cardiac failure should routinely undergo ejection fraction evaluation, and, on the other hand, patients with cardiac failure and a preserved systolic function (the so-called diastolic heart failure) do not tolerate tachycardia and intravascular volume modifications and may develop perioperative problems more frequently than patients with a well compensated cardiac failure, even if with a low ejection fraction.

For this reason, among the available noninvasive tests, the most used are the provocative tests – either effort or pharmacological testing – which, especially when associated with scintigraphy, on the one hand allow us to

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**Table II. Risk of non-cardiac surgical procedures (stratification).**

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<th>High</th>
<th>Intermediate</th>
<th>Low</th>
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<td>Emergency surgery</td>
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<td>Major vascular surgery</td>
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<td>Peripheral vascular surgery</td>
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<td>Surgery generally associated with significant blood loss</td>
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<td>Intraperitoneal</td>
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<td>Intrathoracic</td>
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<td>Orthopedic</td>
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<td>Prostate</td>
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<td>Carotid endarterectomy</td>
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<td>Head and neck</td>
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<td>Endoscopic maneuvers</td>
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<td>Cataract surgery</td>
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<td>Breast surgery</td>
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quantify the patient’s functional capacity and performance, and on the other, to identify the presence of cardiac ischemia with an increasing specificity in relation to the increase in the number of districts involved: from 77% for single-vessel disease to 86% for three-vessel disease. The negative predictive value of effort testing is generally satisfactory. Unfortunately, this test is burdened by some limitations: not all patients are able to perform a physical effort suitable to reach a maximum level of exertion and it is often non-diagnostic. With regard to pharmacological provocative tests (dipyridamole or adenosine followed by thallium scintigraphy), these have many limitations too. First, many retrospective, but only two prospective studies have been published in the literature. Second they revealed a very good negative predictive value (95%), but a low positive predictive value (ranging from 5 to 25%). For this reason, it is necessary to interpret the test results always considering the data in a well known context and, above all, it is not advisable to perform the test routinely. As for the echo-dobutamine test – introduced after thallium imaging – it seems to yield substantially overlapping results with scintigraphy employing dipyridamole in terms of positive and negative predictive values.

Occasionally, noninvasive cardiovascular evaluation could suggest the necessity of coronary angiography (Fig. 1).

**Revascularization**

Having completed the preoperative cardiovascular evaluation, it may be decided that there is an indication to myocardial revascularization, either by means of angioplasty and stent placement or by means of coronary artery bypass grafting. It is thus evident that the revascularization procedure is performed independently of the concomitant indication to non-cardiac surgery. The same guidelines point out that revascularization is performed “to the purpose” of leading the patient to non-cardiac surgery only in particular cases. On the other hand, there is no evidence of the protective role of past angioplasty or bypass against adverse perioperative cardiac events.

Particularly with regard to angioplasty plus stent, another debated topic is the timing of non-cardiac surgery subsequent to the revascularization procedure. The available case histories – still insufficient – reveal an improvement in the prognosis if non-cardiac surgery is performed not before 90 days following the revascularization procedure; surprisingly, however, for a time period between angioplasty and non-cardiac surgery < 90 days, no significant differences in terms of primary events between treated and untreated patients have been reported. Even more recent data – although referring to a limited sample of 40 patients – reveal an increased cardiovascular risk for patients submitted to revascularization who have undergone non-cardiac surgery too early (13 days on average). Out of 40 patients, 8 died, supposedly due to cardiac ischemia, 7 presented with a myocardial infarction, and 11 with major bleeding episodes, most of which occurring in patients submitted to non-cardiac surgery < 2 weeks following angioplasty. Clinical-instrumental evidence revealed that most fatal events were due to thrombosis on the recently implanted stent. On the other hand, obviously the suspension of the antiplatelet therapy, which

**FIGURE 1. Indication to coronary angiography.**

* class I: strong evidence and/or general agreement that the procedure is necessary; class II: divergence of evidence and/or opinion; class III: strong evidence and/or general agreement that the procedure is not necessary.
necessarily precedes the operation, is a high-risk factor for the development of intracoronary stent thrombosis, whereas not suspending it predisposes the patient to major bleeding episodes. The authors, therefore, conclude suggesting a time-span not shorter than 4 weeks between the revascularization procedure and the non-cardiac surgery in order to allow the completion of an efficient antiplatelet treatment.

Discussions concerning the utility of revascularization through coronary artery bypass grafting prior to non-cardiac surgery are mostly based on the CASS (Coronary Artery Surgery Study) file, which constitutes a fundamental database since at the time of enrolment the included patients had been accurately evaluated from the clinical and angiographic points of view. The data extrapolated by Eagle et al. in 1997 showed a low incidence of primary perioperative endpoints (acute myocardial infarction and mortality) for surgical procedures considered as high risk, if patients had previously undergone revascularization through bypass; considering that, however, there was an indication to revascularization independently of the non-cardiac surgery. Patients who mainly benefited from this procedure were those whose CASS enrolment criteria were consistent with unstable angina or coronary artery disease involving more than one vessel and, among these, those > 70 years. However, two important limitations modify and render these data difficult to interpret. First of all, the enrolment in the CASS file dates back to 19 years ago and, in the meanwhile, both coronary artery disease management (even pharmacological management), and the perioperative management of cardiac patients have changed. Secondly, the risk related to the revascularization procedure itself is not taken into consideration. In fact, at present there are no studies comparing the risk of the two surgeries (revascularization and non-cardiac surgery) with that of only one (non-cardiac surgery) performed strengthening the perioperative drug therapy when necessary. Finally, it is not desirable that two surgical procedures (the cardiac and non-cardiac one) are performed in the same surgical session, except for carotid endarterectomy for which, it would be preferable that a cardiac surgeon with vascular surgery skills perform both procedures rather than coordinating two different surgical teams.

The new era

As already mentioned, the major risk of post-surgical cardiovascular complications is myocardial infarction. The causes of perioperative myocardial infarction, however, are probably different from those of spontaneous myocardial infarction. The pathophysiological knowledge of the event is fundamental to implement an adequate perioperative management to reduce the risk. Supposedly, the risk of ischemia or myocardial necrosis is not bound to the surgical stress in itself. In confirmation of that, the major incidence is observed during the second or third postoperative day and it is preceded by a tachycardia peak usually observed on the first/second day. The main determinant, in fact, is the response to surgical stress characterized by an increase in the levels of circulating catecholamines and a prothrombotic tendency. This determines an increase in oxygen demand on the one hand, and, on the other, an increase in the shear stress on the atherosclerotic plaques with consequent possible rupture. On the basis of this premise, it is evident that beta-adrenergic receptor blockers could be effective in reducing the cardiologic risk in view of possible surgery. On the other hand, evidence of this has been provided for more than 10 years and the same guidelines encourage research in the form of prospective studies and suitable case histories aimed at clarifying the protective role of beta-blockers against perioperative ischemic complications. According to some authors, the study of Poldermans et al., even though including only a few patients, marks the beginning of a new era in the perisurgical approach to cardiac patients. According to some studies, as well as to the same guidelines, the imbalance between the extensive dissertation about risk classification and the indication to carry out provocative tests on the one hand, and the recommendation to general cautions in performing non-cardiac surgery on the other, is evident. In other words, the patient’s perioperative management is not significantly modified by the results of these tests and revascularization has a rather limited indication, i.e. that typical for all coronary patients, irrespective of the concomitant need for non-cardiac surgery. Previously to Poldermans’ study, the first randomized study was carried out by Mangano et al. on 200 patients with a high cardiovascular risk candidate to non-cardiac surgery and was published simultaneously to the US guidelines. In this study, the patients were set into two groups randomized to receive placebo or atenolol beginning 2 days before surgery and continued until 1 week after the operation, in such doses as to maintain the heart rate < 65 b/min. Follow-up continued for 2 years. Immediately after the operation, there was no significant difference between the two groups in terms of the mortality due to cardiac causes; however, during the follow-up, a greater percentage of patients surviving free from cardiovascular events was observed in the group treated with atenolol (83%) vs those who received placebo (68%, p = 0.008). The study was contested because of the inequitable distribution of risk factors between the two groups, so that the group treated with placebo turned out to include patients who originally showed a higher risk of developing cardiovascular complications.
On the other hand, the patients studied by Poldermans et al., with a high cardiovascular risk, candidate to major or peripheral vascular surgery, randomized to receive bisoprolol-based therapy (59 patients) or to continue the ongoing therapeutic scheme (53 patients), were perfectly comparable as far as their clinical status, risk factors and perioperative conduct were concerned.

The global mortality due to cardiac causes was 10 times lower in the group treated with bisoprolol (3.4%) than in the follow-up group, and no reinfarction was observed in the 30-day time-span after discharge. The authors concluded that when planning vascular surgery, patients with an echo-dobutamine positive for inducible ischemia and with even one single risk factor should be submitted to beta-blocker therapy starting from at least 1 week before the operation at such a dosage as to maintain the heart rate constantly < 60 b/min. Alternatively, by extending the results of the study, the authors suggest to use beta-blocker-based therapy in all the patients who, on the basis of their clinical evaluation, are found to have an intermediate risk, thus implicitly considering provocative tests unnecessary. The correspondence that followed the publication of this study was very copious and each time characterized by objections, such as that raised by Feldman et al., concerning the too short follow-up duration or the characterization by objections, such as that raised by Feldman et al., concerning the too short follow-up duration or the “dangerous” lesser use of provocative tests. On the other hand, there were those who even exasperated some of Poldermans’ conclusions, maintaining that provocative tests should not be used in the evaluation of the preoperative risk, but that they should be performed only if the clinical evaluation leads to a suspect of concomitant ischemic disease requiring provocative tests might be used for the same patient in order to check the suitability of the therapy and its effectiveness in reducing inducible ischemia or in modifying its onset threshold. Moreover, it must be borne in mind that several studies investigated perioperative beta-blockade, but few of them are randomized and prospective.

Unquestionably, however, if the clinical evaluation leads to a suspect of concomitant ischemic disease requiring diagnostic deepening independently of the indication to non-cardiac surgery, further instrumental investigation should be performed and the advisability of myocardial revascularization should be evaluated. It is obvious that, if the necessity for revascularization is confirmed, non-cardiac surgery should be postponed (except for carotid endarterectomy that necessarily has to precede surgery procedures necessitating an extracorporeal circulation). It is not necessary however, to remind the reader that, both after bypass and after angioplasty, the timing of non-cardiac surgery is of fundamental importance: an operation performed too early (prior to 4 weeks) exposes the patient to a considerably increased risk of perioperative complications.

### Riassunto

La gestione peripersonaria di pazienti a rischio per malattie cardiovascolari candidati a chirurgia non cardiaca è stata a lungo dibattuta nelle precedenti decadi ed è ancora di notevole interesse. Un’adegata gestione peripersonaria può modificare la mortalità e la morbilità postoperatoria e può migliorare la prognosi a lungo termine. Questa rassegna si propone di esaminare le attuali conoscenze riguardo alla valutazione preoperatoria e alla gestione peri e postoperatoria.

Nonostante l’esistenza di linee guida (American College of Cardiology/American Heart Association del 1996) e di numerosi studi sull’argomento, persistono numerose controversie. I principali quesiti riguardano innanzitutto la valutazione preoperatoria attraverso indagini non invasive (ed il reale valore predittivo di aumentato rischio cardiovascolare) e poi l’effettivo beneficio di una rivascolarizzazione coronarica prima della chirurgia non cardiaca. La parte finale di questa review pone l’attenzione su numerose recenti osservazioni cliniche e studi sperimentali riguardo all’efficacia di un esteso utilizzo dei bloccanti dei recettori beta-adrenergici e l’ottimizzazione della terapia farmacologica antischemica nel ridurre il rischio cardiovascolare della chirurgia non cardiaca e nel migliorare la prognosi a lungo termine.

### Parole chiave: Betabloccanti; Chirurgia non cardiaca; Rischio cardiovascolare.
References


