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Cardiovascular

Innovations in management of cardiac disease: drugs, treatment strategies and technology

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Abstract

Within the last generation, the management of patients with heart disease has been transformed by advances in drug treatments, interventions and diagnostic technologies. The management of arterial hypertension saw beta-blockers demoted from first- to third-line treatment. Recent studies suggest that the goal of treatment may have to change to lower systolic blood pressures to prevent long-term organ damage. Today less than 15% of coronary revascularizations are surgical and more than 85% are done by interventional cardiologists inserting coronary stents. Thus, managing patients on dual antiplatelet therapy has become an important issue. With new generations of coronary stents, recommendations are changing fast. In the past, decisions concerning non-cardiac surgery after acute myocardial infarction were based on the delay between infarction and non-cardiac surgery. Today, the main concern is the patient's status in respect of dual antiplatelet therapy after primary percutaneous intervention. There have been advances in the management of heart failure but new drugs (ivabradine, sacubitril/valsartan) and cardiac resynchronization are recommended only in patients with an ejection fraction below 35% on optimal medication. Heart failure remains a major perioperative risk factor. Prospective studies have shown that troponin elevations represent myocardial injury (not necessarily myocardial infarction), are mostly silent and are associated with increased 30-day mortality. Monitoring (troponin assays) for myocardial injury in non-cardiac surgery (MINS) seems increasingly justified. The treatment of MINS needs further research. Technological advances, such as intelligent, portable monitors benefit not only patients with cardiac disease but all patients who have undergone major surgery and are on the wards postoperatively.

Key words: cardiac; drugs; technology

Over the past 25 yr there have been innumerable innovations in the management of cardiac disease, many of which have impacted on the perioperative management of surgical patients. No doubt more innovations are coming and we have to be prepared. As a result of the large number of recent innovations, a selection was chosen for this review with a view of highlighting those most likely to influence clinical practice for adult patients, and particularly elderly patients.

Arterial hypertension

Changing medication over 25 yr

Twenty-five yr ago treatment of hypertension was recommended in patients with blood pressures above 160/100 mm Hg with a target of less than 140/90 mm Hg. First-line antihypertensive agents were beta-blockers and diuretics associated, where necessary, with calcium channel blockers and angiotensin-converting enzyme inhibitors (ACE inhibitors). It was customary

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to maintain all antihypertensive agents up until the day of surgery to avoid the risk of rebound hypertension on their discontinuation. In 2005, evidence from the Anglo-Scandinavian cardiac outcome trial, a randomized controlled trial (RCT) with 19 257 patients, showed that a beta-blocker (atenolol, associated or not with a diuretic) was effective in controlling blood pressure but was inferior to a calcium channel blocker (amlodipine, associated or not with an ACE inhibitor, perindopril) in preventing the long-term damage to target organs.[1] Hence, calcium channel blockers and ACE inhibitors [or if poorly tolerated angiotensin-receptor antagonists (ARAs)] became first-line treatment and beta-blockers were relegated to third- or even fourth-line treatment.[2 3] As a result of the increased use of ACE inhibitors and ARAs, the practice of maintaining drug therapy was questioned. Recent guidelines suggested that stopping ACE inhibitors and ARAs the day before surgery should be considered because of the risk of perioperative hypotension.[4] Data from the VISION study (Vascular events In noncardiac Surgery patients cOhort evaluatioN) showed that withholding ACE inhibitors or ARAs for 24 h before non-cardiac surgery significantly decreased 30-day adverse cardiac events and perioperative hypotension.[5] Future guidelines are likely to advise more strongly withholding these drugs for 24 h before surgery as best management. The direct renin antagonist aliskiren[6] is generally used in patients with hypertension that requires at least two drugs for control. The best association is with amlodipine.[7] However, aliskiren administration can be harmful in patients with type II diabetes as seen in the ALTITUDE trial.[8 9] As it interferes with the renin–angiotensin system, it would seem prudent to withhold aliskiren before surgery. At variance with ACE inhibitors, aliskiren does not have beneficial effects in heart failure.[10]

Evolution of target blood pressures

More recently, the target blood pressure for antihypertensive medication was a blood pressure of less than 140/90 mm Hg. Some recent guidelines have suggested a target of less than 150/90 mm Hg in patients over the age of 60 yr,[11 12] and less than 160/90 mm Hg in those over the age of 80 yr.[13] However, a recent RCT, the SPRINT Trial (Systolic Blood Pressure Intervention Trial),[14] showed that reducing blood pressure to 140 mm Hg systolic was not best management as patients whose systolic blood pressure had been brought down even lower to less than 120 mm Hg by intensified therapy showed reduced morbidity and mortality. A systematic review of target blood pressures has shown, in a total of more than 600 000 patients, that systolic blood pressure less than 130 mm Hg is beneficial.[15] In order to achieve this target, triple or even quadruple antihypertensive therapy is likely to be needed in many patients. Therapy would necessarily include an ACE inhibitor or a ARA. This more intensive therapy is likely to increase the risk of perioperative hypotension.[16] This is of concern as recent evidence shows that pre- and perioperative hypotension is a major risk factor for perioperative cardiovascular complications.[17–19] A very large study with more than 250 000 surgical patients[20] has shown that below a systolic pressure of 119 mm Hg the odds ratio for 30-day mortality starts to increase in the elderly. By contrast, there is no clear limit above which systolic blood pressure increases the odds ratio for mortality. Yet, there is an association between raised diastolic blood pressure and mortality. For the surgical patient the question remains: 'perioperative blood pressure: what is too high, too low, or just right?' as stated in the editorial commenting on the above paper.[21] The risk associated with low systolic blood pressure may not be surprising as in a large study in more than 22 000 patients with known coronary artery disease lowering blood pressure below 120 mm Hg systolic and 70 mm Hg diastolic was harmful over a five yr period.[22]

Thus, with hypertension there have been three phases. When treatment was rather ineffective, hypertension was a significant risk factor for perioperative adverse cardiovascular events; with improved treatment, hypertension ceased to be considered a significant risk factor, to the extent that it is not even mentioned in the American College of Cardiology/American Heart Association (ACC/AHA) guideline 2014.[23] However, with more intensive management of hypertension with targets of 120 or 130 mm Hg for systolic blood pressure, hypertension may again become an important risk factor because of the possibility of drug-induced perioperative hypotension. We will have gone full circle!

New concepts in the pathophysiology of hypertension

Considering the future, it is possible that the approach to the treatment of hypertension could be affected by new findings suggesting that the pathophysiology of hypertension includes changes in the activity of neuronal nitric oxide synthase (nNO synthase). There is evidence for the role of nNO synthase in the control of blood pressure[24] and of the coronary circulation.[25] A small study has shown that inhibition of nNO synthase in healthy human subjects increases arterial blood pressure.[26] If this is confirmed in larger studies, it may stimulate development of new pharmacological agents capable of stimulating nNO synthase.

Coronary revascularization

The rise of percutaneous coronary interventions

In 1992, 20 000 patients underwent surgical coronary revascularization in the UK while only 10 000 underwent percutaneous coronary angioplasty; of these only 319 received bare metal coronary stents.[27] Five yr later, the numbers of surgical (20 000) and interventional (20 000) coronary revascularizations were equal. Sixty per cent of interventions involved insertion of bare metal stents (BMS).[28] The 2015 British Cardiovascular Intervention Society (BCIS) audit shows that 16 500 surgical and 97 000 interventional coronary revascularizations were performed; 88.5% of the latter using drug-eluting stents (DES) and only 11.5% using BMS.[29] With both types of stents there is the problem of managing dual antiplatelet therapy (DAPT) in surgical patients. The risk of stent thrombosis if DAPT is stopped, and the risk of excessive bleeding if it is maintained must be carefully evaluated, together with the risk involved in delaying non-cardiac surgery. The recommendation is, whenever possible, to delay non-cardiac surgery until DAPT is no longer needed (12 months after acute coronary syndromes irrespective of the type of stent, probably six months for stable angina for DES, and four weeks for BMS) according to recent guidelines.[4 23] The most recent guideline of the ACC/AHA[30] clarifies the duration of DAPT (Fig. 1).

Non-cardiac surgery in patients with coronary stents

The same guideline[30] clarifies the delay between insertion of stents and non-cardiac surgery (Fig. 2). For BMS, more than 30 days is recommended before non-cardiac surgery; for DES, more than three months is recommended before surgery is to be considered, preferably waiting for six months before

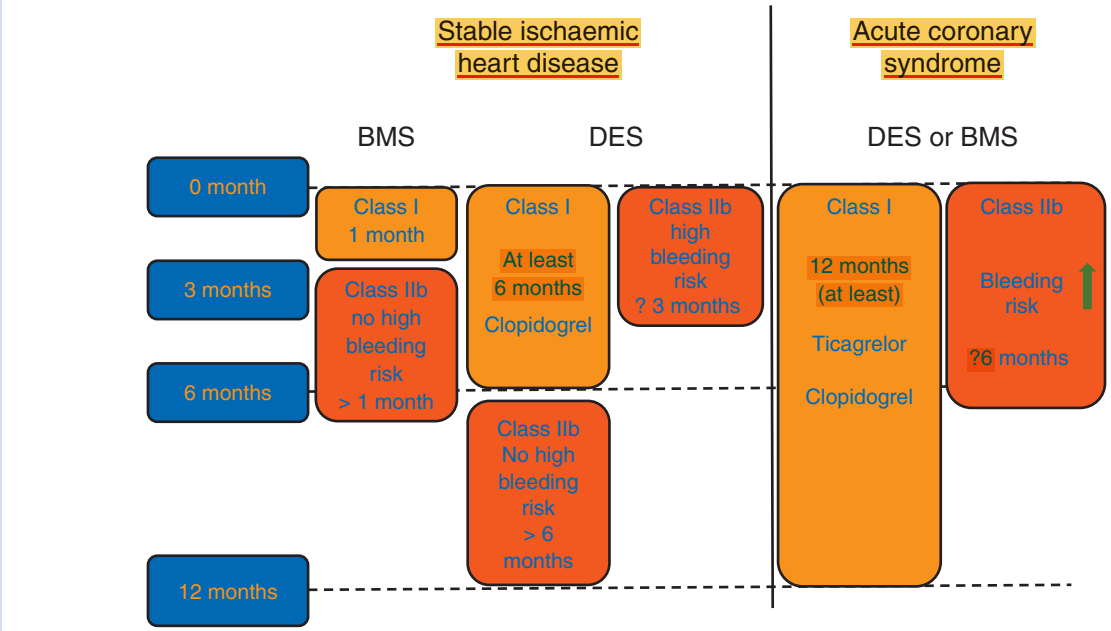

Fig 1 Recommendations for dual antiplatelet therapy after insertion of coronary stents according to the 2016 ACC/AHA guideline (redrawn from Levine and colleagues. *J Am Coll Cardiol* 2016; 68: 1082–115,[30] with permission). BMS, bare metal stent; DES, drug eluting stent.

proceeding. However, there is still an important question that is not addressed as clearly as it should. After an acute coronary syndrome, it is recommended to continue with DAPT for one yr irrespective of the type of stents. Does the algorithm in Figure 2 apply to these patients? The guideline is silent on this question.

For some patients, there may be significant risks in delaying non-cardiac surgery. Studies published between 2009 and 2011 showed the risk of non-cardiac surgery in patients with coronary stents to be very high during the first six months after stent insertion.[31 32] With second- and third-generation DES, recent studies suggest that the risk is already substantially reduced three months after stent insertion,[33–35] and may not be very different from the risk of non-cardiac surgery in patients without coronary disease who undergo non-cardiac surgery. Thus, the most recent guideline suggests that it is safe to proceed with non-cardiac surgery six months, and if clearly necessary, even three months after DES insertion.[30]

An important question is the safety of neuraxial blockade in patients receiving antiplatelet therapy, irrespective of its reason. A specific guideline on this topic is clear: apart from aspirin (and only when no heparin is used) neuraxial blockade should not be used in the presence of ongoing antiplatelet therapy.[36 37] In respect of antiplatelet therapy with clopidogrel alone, a study in vascular surgical patients has shown the absence of complications.[38] However, the authors state: 'owing to the small sample size, we cannot recommend the liberal use of epidural analgesia with on-going clopidogrel administration'. Thus, the guideline stands.

Where managing patients on DAPT, it should not be forgotten that spontaneous bleeding occurs. As an example, a study of over 8000 patients with spontaneous intracranial haemorrhage has shown dual antiplatelet to be a major risk factor and to have an adverse effect on outcome.[39] As some surgical procedures can be carried out while patients receive DAPT, the possibility of a spontaneous bleeding complication *outside* the surgical field must be kept in mind during the perioperative period.

Do coronary stents protect against cardiac complications of non-cardiac surgery?

While the 2014 European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA) guideline states that patients with coronary stents remain at higher risk,[4] the 2014 ACC/AHA guideline considers data to be inconclusive.[23] In the light of recent studies, insertion of drug-eluting coronary stents may prove to be protective.[34] Indeed, the study by Egholm and colleagues[35] showed that the risk of 30-day myocardial infarction in patients with DES inserted within one yr of surgery was higher than the risk in patients without coronary artery disease only for the first two months after stent insertion. The study's 4303 stented patients were matched with 22 232 controls. This study suggests that insertion of coronary stents may protect against perioperative major adverse cardiac events.

It is generally recommended to maintain DAPT or at least aspirin whenever possible.[30] Unfortunately the literature is confusing as some studies show the risk of adverse events to be the same whether DAPT is stopped or maintained.[34 40] The most recent study that has addressed this issue, based on over 1082 patients who underwent cardiac and non-cardiac surgery after insertion of stents (63% DES), concluded that antiplatelet discontinuation increases the 30-day risk of major cardiovascular adverse events (MACE), while not offering significant protection from major bleeding.[41] Moreover, a small study of 201 subjects suggests that the incidence of MACE is high in patients undergoing non-cardiac surgery after previous percutaneous coronary

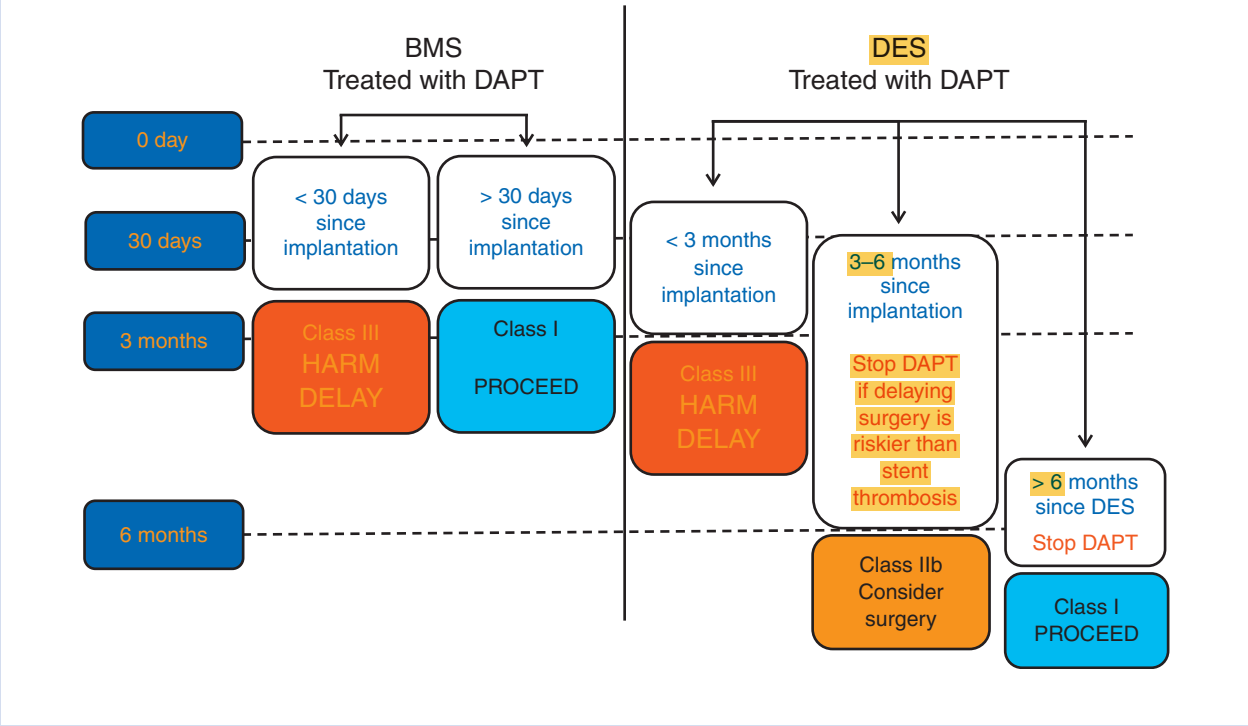

Fig 2 Recommendations for non-cardiac surgery after insertion of coronary stents according to the 2016 ACC/AHA guideline (redrawn from Levine and colleagues. *J Am Coll Cardiol* 2016; **68**: 1082–115,[30] with permission). BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent.

intervention in spite of adequate perioperative antiplatelet therapy.[42]

For the management of patients with coronary stents, the 2016 ACC/AHA guideline reiterates that 'decisions are best determined by a consensus of the surgeon, anesthesiologist, cardiologist, and patient.'[30] There is a need to consider the time that elapsed since percutaneous coronary intervention (PCI) with stent insertion, the type of stent, the risk of severe bleeding, the risk that even limited bleeding may negate the benefits of surgery (closed cavity surgery) and the risk of stent thrombosis if DAPT is stopped.

Future stents

There has been huge investment in the development of coronary stents with novel vascular skeletons and newer eluted drugs. Recovery of vascular function as the vascular skeleton is resorbed may prove to be a significant advance. However, this is not yet proven.[43] Moreover, recent studies show a significant risk of late thrombosis.[44 45] Thus, the duration of DAPT in a patient with a resorbable skeleton may have to be longer that with metal skeleton DES. It may have to be as long as three yr,[46] with a substantial risk of bleeding complications.

Surgery in patients with previous myocardial infarction

Forty yr ago, the introduction of fibrinolysis revolutionized the treatment of acute myocardial infarction[47 48] and, where complemented by early beta-blockade, significantly reduced its mortality as shown in the ISIS1 study.[49] With this approach the management of patients presenting later for non-cardiac surgery after myocardial infarction was simple: sufficient time needed to have elapsed before elective non-cardiac surgery. Gradually the delay was reduced from six to three months, or even six weeks if there was no ischaemia on a stress test.[50] The introduction of primary percutaneous coronary intervention (PPCI) transformed the management of acute myocardial infarction. It is undoubtedly a great success but it means that of 100 000 UK patients receiving mostly DES annually in the UK, 60 000 receive them because of an acute coronary syndrome [ST-segment elevation (STEMI), non-ST-segment elevation myocardial infarction (non-STEMI)] and will be on DAPT for 12 months. As 10% of patients need non-cardiac surgery within one yr of stent insertion,[34] at least 6000 will present for non-cardiac surgery in the first year after PCI for myocardial infarction. Recent studies show that patients are at very high risk for postoperative cardiac complications if operated on less than three months after receiving stents for myocardial infarction.[51 52]

In the longer term, there may be a decrease in the number of patients suffering acute myocardial infarction. Plaque rupture is a major cause of acute coronary events. It could be prevented by therapies aimed at reducing apoptosis of smooth muscle. Smooth muscle constitutes a very important part of the interface between the thrombogenic core of atheroma and the lumen of the vessel. Reducing its destruction would reduce the risk of plaque disruption. There is experimental evidence that it is possible to strengthen this interface so that plaques become less likely to rupture.[53 54]

Heart failure

Pharmacological advances in the treatment of heart failure

Heart failure has a bad prognosis and, in the surgical setting, is the worst risk factor for adverse perioperative cardiac events.[55 56] Over the past 25 yr its medical treatment has progressed with the use of ACE inhibitors, beta-blockers and more recently aldosterone antagonists, while digoxin is given only to patients in whom management of atrial fibrillation by more active drugs is poorly tolerated. Innovations have included a brain natriuretic peptide (BNP) analogue (nesiritide) but results were disappointing.[57] Ivabradine, a blocker of the 'funny' channels in pacemaker cells, reduces the I_f current so that the spontaneous depolarization of the cells becomes slower and heart rate decreases. The slower heart rate is favourable in ischaemic heart disease and in heart failure. More recently, sacubitril/valsartan has been introduced. Sacubitril is a blocker of neprilysin, the enzyme that degrades both atrial and brain natriuretic peptides. Thus, more of these peptides remain active and contribute to improving cardiac function; the beneficial effects are reinforced by the afterload-reducing properties of the ARA valsartan.[58] However, it is important to note that guidelines prepared by the National Institute for Health and Care Excellence (NICE)[59 60] recommend ivabradine and sacubitril/valsartan only in patients on optimal heart failure medication and with an ejection fraction of less than 35%. Although treatment of heart failure has progressed, mortality remains very high: 20% at one yr, 50% at five yr and 70% at 10 yr.[61]

Resynchronization therapy

Dyssynchrony of ventricular contraction decreases its pumping efficiency. This can be overcome by the use of cardiac resynchronization devices.[41] Such devices often associate a cardioverter-defibrillator and/or a cardiac pacemaker and improve the survival of selected groups of patients as a high proportion of deaths among patients with heart failure occur suddenly and unexpectedly because of electrical disturbances in their myocardium.[62] These complex devices are recommended only in patients with an ejection fraction less than 35%.[62 63] The development of leadless pacemakers and dual chamber stimulators may facilitate their use and prevent problems associated with intracavitary leads.[64]

Challenges for the future

There is still a large number of patients who have advanced heart failure with poor prognosis despite optimal medical therapy. The number of patients is increasing because improved management of acute myocardial infarction has reduced its early mortality. This has led to an epidemic of heart failure as more people survive the initial episode but suffer from significant cardiac dysfunction.[65] Thus, the burden of heart failure is growing.[66]

Mechanical assistance of the heart started with the intra-aortic balloon pump almost 60 yr ago[67] and led to the development of ventricular assist devices. Today great progress has been made with left ventricular assist devices, now used as life-long support, rather than bridge to heart transplant.[68] However, mechanical assistance of the heart is still associated with some disability in the form of lifestyle limitations. For this reason, cellular repair of the myocardium is becoming an important area for research. The greatest advances in the management of heart failure are likely to be the introduction of techniques for inserting bone marrow cells into the damaged myocardium and promoting vessel growth.[69–73] An alternative approach is the development of small molecules that 'direct' the development of stem cells into myocytes.[74 75] These new therapies may still be some years away but would offer true repair of damaged myocardium. They may also offer hope to patients with angina that is refractory to conventional medical treatment and in whom coronary revascularization cannot be considered.[70]

Biomarkers

Detection of silent myocardial damage and implications: the concept of myocardial injury in non-cardiac surgery (MINS)

For many years there was considerable interest in perioperative silent myocardial ischaemia as recorded by ambulatory ECG monitors. Silent ischaemia is very frequent in surgical patients.[76 77] However, its association with peri- and postoperative adverse cardiovascular events is variable. By contrast, studies of cardiac biomarkers such as troponins show a strong association between elevated levels and adverse outcome.[78] The VISION study, with over 15 000 patients,[79] showed increases in fourth-generation troponin T (TnT) to be *consistently* associated with postoperative mortality. Even modest elevations, much lower than the level regarded as indicative of myocardial infarction, predict 30-day mortality. Modest elevations of TnT indicate the presence of myocardial injury. MINS is characterized by TnT above 0.03 ng litre^{-1}.[80] Most frequently, this modest elevation is not associated with clinical signs of myocardial ischaemia. Thus, injury would be unrecognized in the absence of routine troponin assays. High-sensitivity TnT (hs-TnT) levels, as observed in 21 000 patients, confirmed the prognostic role of elevated troponins with a mortality of 9.1% for hs-TnT between 65 and 1000 ng litre^{-1} and 29.6% for hs-TnT above 1000 ng litre^{-1}.[81] Similarly, elevations of troponin I (TnI) after major non-cardiac surgery are associated with a considerable increase in postoperative death, especially within the first six months after surgery.[82] In non-cardiac, non-vascular surgery, a systematic review based on 11 studies with 2123 patients has shown odds ratios for 30-day and 1 yr mortality of, respectively, 3.53 (95% CI 2.21–5.62) and 2.53 (95% CI 1.20–5.36), and for major adverse cardiac events of 5.92 (95% CI 1.67–20.96) at 30-day and 3.00 (95% CI 1.43–6.29) at 1 yr.[83] Age may play a role in the association between elevated troponins and outcome as a relatively small study in elderly patients with hip fracture has shown that isolated troponin I elevation was not associated with adverse outcome while a clinical acute coronary syndrome was.[84]

Monitoring troponins and managing their rise

While the 2014 guidelines suggested that postoperative troponin assays may be useful in very high-risk patients,[4 23] a 2017 Canadian guideline recommends to obtain daily troponin measurements for 48–72 h after non-cardiac surgery in patients with baseline risk of more than 5% for cardiac death or non-fatal myocardial infarction.[85] A clear strategy for the management of patients with MINS is needed. Studies show that many of the patients who develop MINS suffer from cardiovascular disease but are not on optimal therapy. The first approach is to optimize their treatment. This may be achieved by adding agents they should receive as part of their long-term medication, or increasing the

dosage of the appropriate medications, including beta-blockers, statins, ACE inhibitors and an antiplatelet agent (often aspirin) if doses are inadequate.[86 87] The effectiveness of this approach has been demonstrated in a small (proof-of-concept) study: it decreased the risk of adverse events.[86] More data are needed.[88] Recent studies have shown that even in patients clearly at risk for ischaemic heart disease only a relatively small proportion receive optimal treatment.[17 82 89 90] After POISE[17] and the most recent data on the benefits of withholding ACE inhibitors and ARAs in hypertensive patients presenting for non-cardiac surgery,[5] it may seem paradoxical to propose their introduction to intensify treatment in patients with elevated troponins. However, the context is completely different. In the face of clear evidence of myocardial injury beta-blockers and ACE inhibitors are given for the treatment of an ischaemic event as they would be under non-surgical settings where their benefits are undoubted.[91 92]

As the adverse role of MINS is better recognized this will stimulate research in novel therapies that may include coronary revascularization, or the prolonged administration of dabigatran, currently investigated in the MANAGE trial.[93] As pharmacological protection against perioperative cardiovascular events is elusive, with the exception of statins,[94] it may make more sense to monitor patients postoperatively (troponin assay, ECG) and develop effective strategies to treat myocardial injury.

BNP and N-terminal prohormone of brain natriuretic peptide (NT-proBNP)

BNP and NT-proBNP fragments are released from the myocardium in response to a complex integration among mechanical, chemical, haemodynamic, humoral, ischaemic and inflammatory inputs.[95 96] Assays for these molecules have been used for nearly two decades as markers of heart failure.[97] Point-of-care assays are extremely useful in emergency departments. However, these biomarkers have been used less frequently in the context of perioperative medicine. Yet elevated BNP or NT-proBNP are very useful markers of cardiac dysfunction and correlate with adverse outcome. Associated with the revised cardiac risk index (RCRI), they better identify patients at high risk.[98] Moreover, elevated B-type natriuretic peptide predicts 30-day and over 6 month outcome in non-cardiac surgery.[99 100] Thus, pre- and postoperative monitoring of BNP or NT-proBNP may help to identify patients at very high risk and facilitate their pharmacological management.

The field of biomarkers is expanding and elevation of presepsin, a humoral marker for systemic inflammatory response syndrome and sepsis, is associated with increased 30-day, 6 months and 2 yr mortality in cardiac surgery patients.[101]

Technological advances

Transcatheter aortic valve implantation (TAVI)

Preoperative aortic valve replacement before non-cardiac surgery is based on the severity of the stenosis and accompanying symptoms. The introduction of TAVI has not changed the indications but has made it possible to offer the intervention to patients in whom the risks of surgical repair would be too high. Indeed, a 2017 NICE guideline states that 'TAVI offers a potential treatment for patients with aortic stenosis for whom surgical aortic valve replacement would not be suitable.'[102]

The 2015 BCIS Audit shows that over the period extending from 2007 to 2015 the number of TAVI has grown from 66 in 2007 to 2473 in 2015. The mean age of patients was 81 yr. The 30-day mortality has decreased from nearly 14% in 2007 to less than 4% in 2012.[103] As the risk of the procedure decreases, more elderly patients may be offered TAVI. This may reduce the number of patients with significant uncorrected aortic stenosis presenting for non-cardiac surgery.

Many types of valves have been developed. Some are self-inflating whereas others are balloon inflated. The valve itself is made of biological material attached to a metallic structure. Femoral and subclavian arteries are used for their insertion. Increasingly the procedure is carried out under local anaesthesia with or without some additional sedation unless valve insertion is through the apex of the left ventricle via a small thoracotomy.

Transcatheter mitral valve replacement (TMVR)

TMVR may be an option for selected patients with severe mitral regurgitation. This intervention may help address an unmet need in patients at high risk for non-cardiac surgery. Several systems have been developed.[104] A potentially simpler technique consists in the advancement of a clip positioned in the middle of the regurgitant valve such that blood flows on both sides of the now split mitral orifice.[105] However, progress has been slow in the UK as three implantations were performed in 2008 and still only 86 in 2015.[29]

Pharmacogenetics

While we expect a 100% efficacy with an i.v. induction agent and with agents for the maintenance of anaesthesia, outside anaesthesia most drugs do not cure 100% of the patients they are designed to treat. It is quite possible that, on occasion, the lack of efficacy relates to the genetic make-up of patients. With clopidogrel, the risk of adverse cardiovascular events is, for example, higher in patients with cytochrome P450 2C19 polymorphism as this decreases its antiplatelet activity.[106] In the treatment of heart failure beta(1) AR-389 variation alters signalling and affects therapeutic responses to beta-blockers.[107] For statins, variants in SLCO1B1 are strongly associated with an increased risk of statin-induced myopathy.[108] Altered efficacy and patterns of side-effects are likely to play an important role with many drugs. Advances in pharmacogenetics will make it possible to personalize treatments.[109]

Telemonitoring

Ambulatory monitoring of myocardial ischaemia has been available for many years. Ambulatory monitoring of blood pressure has become an essential tool in the diagnosis of arterial hypertension before initiating treatment but it is not yet wireless. By contrast, ECG telemonitoring has entered out-of-hospital practice and transmits relevant events outside the hospital environment to a specialist centre. It is an important tool in the diagnosis of myocardial infarction before admission to hospital, and to the detection and management of severe arrhythmias. The most recent implantable cardioverter-defibrillators can be remotely 'interrogated' where patients are close to a remote captor system so that events can be analysed.

Many wrist-watch-size blood pressure monitors are under development. They are based on the principle of analysing the waveform at the level of the radial artery, without any need to stop blood flow. The data include systolic and diastolic blood pressures and heart rate. While monitors work well under resting conditions, their reliability during exercise remains to be demonstrated. Transmitted via a mobile phone, data can be

remotely downloaded for examination. Such devices could play an important role in the preoperative assessment of hypertensive patients as data collected over a few days would be more reliable than isolated readings. However, as with all technical advances there is a cost attached to them and there is a need to demonstrate that using such devices is cost-effective.

On the wards, early warning score systems have become an essential part of patient management. While current vital signs such as systolic and diastolic blood pressures, respiratory rate, heart rate and temperature are in general use, detection of trends increases the accuracy of models designed to detect critical illness on the ward.[110] Electronic data collection makes this possible and facilitates identification of at-risk patients by remote interrogation of the data. The development of easily wearable and reliable ECG, pulse oximetry and blood pressure monitors, with data transmitted wirelessly to a central server, will make it possible to monitor mobile patients on the ward,[111] and institute treatment in good time to prevent adverse outcomes.

Cardiac investigations

While cardiac catheterization and coronary angiography are invasive gold standard investigations, radionuclide assessment of the coronary circulation, computed tomography (CT) including CT angiography and cardiac magnetic resonance imaging (CMR) continue to expand and their indications to extend. Thus, more and more information is becoming available non-invasively.

The initial phase of CMR collects data on four long-axis, one short-axis and an aortic valve short-axis view according to a standardized acquisition protocol that is used worldwide.[112] Thus, basic structure and function can be easily determined and result in narrower normal reference ranges that make it easier to identify abnormal phenotypes.[113] Adoption of CMR in clinical practice was stimulated by the introduction of compounds for contrast enhancement, most commonly gadolinium-based. Such CMR contrast agents shorten the relaxation times of nuclei within body tissues following oral or i.v. administration. The late gadolinium enhancement (LGE) technique allows visualization of infarction and assessment of the potential for functional recovery.[114] It also informs on disease aetiology. Scar extent predicts the risk of heart failure. LGE can be used as a surrogate endpoint to evaluate the efficacy of therapeutic interventions.[115] In addition, stress perfusion using adenosine can detect significant coronary stenoses.[116]

Conclusions

In the last 25 yr considerable innovation in the management of cardiac disease, drugs, treatment strategies, and technology has taken place. More innovations can be predicted and the changes are likely to accelerate over the next 25 yr. What seems to be almost science fiction today may then be daily routine!

Declaration of interest

No relevant interests.

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