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THE EVOLVING MANAGEMENT OF UNSTABLE CORONARY ARTERY DISEASE AND ITS IMPACT ON PRACTICE OUTWITH THE TERTIARY HOSPITAL

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Chest pain due to underlying coronary artery disease forms a major aspect of acute medical referrals to hospital from the community. Increasingly, attention is now being focused on the identification and management of 'high-risk' cardiac patients prior to the diagnosis of infarction in an attempt to avert the loss of myocardium and its sequelae. This differs critically from infarction management, where any strategy which is adopted can only limit the loss of heart muscle. Unstable coronary arterial disease can present in various ways but has the common denominator of non-fatal or fatal myocardial infarction at its conclusion. While myocardial infarction frequently represents coronary occlusion, unstable angina comprises a complex of pathological conditions including platelet aggregation, thrombus formation and fixed and/or dynamic coronary arterial restrictions. Occlusion and infarction may occur during the course of the current admission, or patients may enter repeated cycles of instability which will eventually culminate in infarction after a variable period. The current large range of developments for the hospital care of such patients will be considered and discussed.

THE CORONARY CARE UNIT AS A FOCUS FOR MANAGEMENT

Coronary Care Units (CCU) are established for the management of patients with coronary arterial pathology during the evolution of myocardial infarction, for the continuation (but not necessarily the initiation) of fibrinolytic or other re-perfusion therapy, and for the management of rhythm or pump failure sequelae. CCU may be equally, or even more, important in the management of unstable coronary disease in that greater potential benefits may be derived by these patients. The overall risk for patients with an uncomplicated and treated inferior infarction is less than in those with unstable coronary disease, yet the latter patients can often be denied a CCU bed in preference to a patient with a stable infarct.

What are the benefits of CCU admission for this patient group? The key is effective monitoring and patient stratification to distinguish those at highest risk of developing infarction from those whose risk is less, and indeed from those in whom the risk can be considered as negligible.

Although formally untested, high medical and nursing staff ratios intuitively allow more attention to be given to individualised assessment. Patient selection for CCU can be based on symptoms, electrocardiographic findings or biochemical measurements. These assessments are all facilitated by becoming focused in a CCU. The structured assessment of cardiac risk by history taking and physical examination, and access to important ancillary specialist investigation (such as immediate echocardiographic assessment) are powerful tools for patient stratification. Although the cost-effectiveness of clinical stratification awaits definition, the potential clinical and resource benefits in focusing investigation and therapies on the right patients and allowing safe discharge of others, are substantial (see below).[1]

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Symptoms

Increased frequency and/or severity of symptoms or pain at rest define unstable coronary disease clinically. While chest pain or other cardiac symptoms are important markers and there may be a tendency for over-reporting of symptoms, this is to be preferred to under-reporting. Yet symptoms *per se* remain an inefficient marker of anatomical instability, being neither particularly sensitive (significant numbers of patients with unstable coronary problems can be asymptomatic) nor specific (significant numbers of symptomatic patients have normal coronary arteries).

Among the patients who present to hospital with chest pain of unknown origin, simple clinical factors can be used to identify those at high risk of having myocardial ischaemia or infarction as the cause of pain. The most powerful predictor is a pain history typical of myocardial ischaemia and occurring at rest. A structured assessment of symptoms can be formulated based upon the probabilities of ischaemia/infarction outcomes observed in population studies.[2,3] Although the anatomical severity of coronary disease may not be accurately predicted in individual patients,[4,5,6] prospective studies of the use of structured symptom assessment suggest that predictions of outcome are broadly accurate.[2]

Electrocardiography

A careful assessment of the ECG remains a critical aspect of management. While eventual outcomes for patients selected only on the basis of unstable symptoms can be variable, evidence of electrical instability carries significant adverse prognostic weight. Patterns such as reversible T wave changes, ST elevation or depression with or without reciprocal change, or transient rhythm or conduction change, are well-established prognostic predictors. The most powerful indicator of adverse outcome is the new onset ST segment deviation or left bundle branch block on admission. T wave inversion alone seems not to add significantly to the clinical history in predicting outcome.[7]

Ideally, ECG data are based on a 12-lead study performed when symptoms occur: a reading obtained when the cardiographer does the CCU ward round is much less instructive. While finding ECG changes during pain is facilitated by CCU observation, this is still not ideal as assessments can be affected by immediate therapies (such as sub-lingual nitrate or pain relief by opiate) or the intermittent nature of the electrocardiographic sampling. Electrocardiography is, therefore, a highly specific but a poorly sensitive triage tool.

Any modern CCU facilitates ECG data collection on a continuous basis. Currently, continuous ECG recordings obtained routinely are hardly ever used except in conjunction with automated detection (and usually print documentation) of major rhythm abnormalities. Transient rhythm disturbance is rarely noted, and coupled ectopy is often ignored despite the well-established association of multiform ectopy to ischaemia. Yet these records can provide valuable clues to functional and anatomical coronary instability if the continuous nature of the data is explored. One or two channels of ECG (most modern systems have multiple-lead capacity dependent on the numbers of channel inputs) recorded continuously can increase both the sensitivity and specificity of ECG data in the presence or absence of symptoms. During clinical trial studies, continuous ST segment monitoring for transient electrocardiographic ischaemia has been shown to be the strongest predictor of adverse prognosis, retaining its independent predictive value on multivariate analysis.[8]

The number, timing, duration and resolution of ST deviation events are analysed in the same way as in the assessment of ambulatory ischaemia during Holter monitoring. Such changes reliably reflect ischaemia but are not necessarily anatomically accurate.

They can reflect remote ischaemia in the presence of triple vessel disease.[9] Such analyses are potentially available in the majority of CCU but the facilities to integrate continuous ECG with automated ST analyses, while equally available in many forms, is rarely used in practice.

Biochemistry

The use of newer, more sensitive and specific biochemical markers of myocardial damage is now having an impact on the early stages of diagnosis of ischaemia and infarction. The increased availability of the MB-CK isoenzyme assay is a notable step forward over total measurement. However, even this assay may not be sufficiently sensitive for the identification of unstable coronary disease (with no infarction) in unselected patients with chest pain.

The measurement of cardiac troponin is being increasingly used as a tool to provide greater sensitivity and specificity in the detection of patients with acute coronary syndromes short of infarction, or to accelerate the early detection of infarction in evolution. The quantitative reliability limit of such assays is the limiting factor in its use for accurate triage of patients early. The combined measurement of both troponin T and troponin I may be valuable. Although not yet able to absolutely exclude an increased risk of cardiac event, both fractions have differing quantitative profiles (with TnT rising to >1 ng/ml later than TnI in infarction); both seem broadly more sensitive, but not more specific, than MB-CK elevation. An alternative view that these markers may even be too sensitive has been voiced, and possibly they could change the definition of myocardial infarction from the accepted combination of clinical/electrocardiographic and biochemical evidence to biochemical changes alone.

A variety of other markers and mediators of acute inflammation arise during coronary artery occlusion and unstable angina. C reactive protein, for example, has been established for some time as a marker of a poor outcome in patients who symptomatically settle after an episode of unstable angina.[10] Yet the sensitivity and specificity of this assay remains to be established[11] and it is currently probably not of major practical value.

Overall management strategies clearly need to be based on combinations of the above criteria, with triage occurring in suitably-monitored environments. Due to the sheer numbers of patients involved it is essential that patient dispersal is controlled, and that cardiac care be focused on those who are candidates for effective therapies to avert infarction.

Caring for the patient with unstable coronary syndrome:

- Patients with unstable coronary syndrome are common and at high risk of infarction.
- Non-cardiac pathologies need to be separated efficiently from true cardiac problems.
- Coronary Care Units may be a more appropriate place to care for unstable angina than for some low-risk established infarctions.
- Patients at risk of infarction need to be stratified on the basis of:
  - cardiac risk factors,
  - continuing symptoms,
  - electrocardiographic indices of ischaemia (preferably on a continous ECG reading),
  - sensitive and specific biochemical markers (measurement of cardiac troponins) but most probably on a combination of factors.

THE ROLE OF CORONARY ARTERIOGRAPHY

After establishing myocardial ischaemia as the diagnosis, definition of coronary anatomy is a critical step. For the forseeable future this will still have to be achieved by contrast coronary arteriography, and facilities for this investigation are increasingly available in most large UK hospitals. Angiography is a safe and effective investigation in an elective setting, associated with minimal, but definable, risks of significant procedure-related adverse events. (»0.1% death/stroke/MI).[12,13] This must be distinguished from the higher rates of complications associated with interventional procedures or investigation of unstable patients for which separate specific figures are not easily available.

The use of coronary arteriography in the initial assessment of acute coronary syndromes is difficult to assess, and must be clearly separated from studies of catheter-based interventional treatments for myocardial infaction which have higher procedural complication rates. The efficacy of such interventional achievements remains controversial and is the subject of ongoing study in tertiary hospitals where both high-volume (i.e. experienced) interventional operators and/or cardiac surgical back-up are available. Thus there is little hard data on which to base management decisions (such as to recommend acute intervention) for the majority of clinicians practising in a non-tertiary hospital. Current investment is allowing increasing access to diagnostic cardiac catheterisation in many larger district hospitals, but interventional procedures are probably not appropriate from a safety standpoint in this setting. Future research may suggest that these procedures be feasible in the district hospital but there remain important practical problems of patient safety, outcome quality in low volume operators and overall cost benefit to be overcome.

Non-ionic contrast media are now widely used in elective angiography due to the reduced frequency of adverse reactions to them and/or reduced radiation doses required for imaging.[14] However, recent experience in unstable coronary disease during attempted catheter-based intervention would suggest that this form of contrast agent may be responsible for inducing abrupt vessel closure. Accordingly, it may be best avoided in favour of ionic media in this setting. Spontaneous closure of coronary arteries during catheterisation is an established, albeit rare, phenomenon which can occur in patients with ostensibly normal coronary arteries, at least at angiography. While there is little published evidence to suggest that this event is, or is not, more frequent during investigation of patients with unstable angina than in others, this is nonetheless a widely-held view. As abrupt vessel closure is a clinical emergency, resulting in fatal or non-fatal myocardial infarction, it is obviously an area onto which research requires to be focused as there are implications for the role of arteriography outside centres with surgical or interventional cardiology backup.

Normal or only minimally diseased coronary arteries are an important finding in this group of patients. While these patients occupy as many as one-third of all diagnostic coronary arteriography in the USA, they have an excellent long-term prognosis regardless of continuing chest pain or disability.[15] The proportion of unselected patients with normal coronaries, despite typical chest pain, is not decreasing with time. Angiographically-proven progression of atherosclerosis, which is common and clinically significant in 20-30% of a population of patients with coronary artery disease, is rare in those with a normal angiogram, particularly if female.[16] Such a finding in a clinically unstable patient can provide considerable reassurance for patient and physician, and reduce repetitive re-admission rates in favour of out-patient investigation. This can lead to an obvious reduction in the overall costs of care.

The role of diagnostic arteriography:

- Diagnostic coronary arteriography is a simple and important investigation in unstable angina.
- General safety is well-established for elective myocardial ischaemia but is less well defined for the clinically unstable population. This may affect the elective site of investigation.
- For local investigation, patients may need to be stratified on the basis of continuing pain problems but with:
  - no associated electrocardiographic indices of ischaemia (preferably on continuous ECG recording),
  - no rise in biochemical markers (measurement of cardiac troponins).
- Ionic contrast media may be preferable in the unstable setting.

ADVANCES IN PHARMACOLOGICAL MANAGEMENT

Aspirin and heparin as a 'gold standard'; LMWt heparin and new antithrombins

The efficacy of the combination of aspirin (ASA) and heparin as compared to isolated individual therapies has been established across multiple studies.[17] Heparin administration is essential in acute management while unfractionated heparin, if used, is probably best administered intravenously rather than sub-cutaneously; although the efficacy of subcutaneous heparin is nearly equivalent, bleeding complications are not greatly reduced.[18] Low molecular weight heparins prescribed instead of unfractionated heparin appear to have an advantage in some studies, but less or none in others.[19,20,21] Extended therapy with subcutaneous low molecular weight heparin apparently gives fewer additional benefits over and above those seen in managing the acute event (six days).[22] However, overall subcutaneous low molecular weight heparin can at least be viewed as a viable alternative to intravenous heparin in the acute management of unstable coronary syndromes. An undeniably important aspect of its routine use, instead of intravenous unfractionated heparin, is the total management costs. When the reduced financial costs of monitoring an unfractionated heparin infusion are combined with the reduced costs of revascularisation by catheter or surgery, then the use of low molecular weight heparin may be the more cost-effective treatment.[23] Even accepting this anaysis, the immediate impact of adopting low molecular weight heparin on the district hospital medicines bill can be substantial.

In parallel with the development of low molecular weight heparin, the search goes on to refine anti-thrombotic therapy with newer agents. Direct thrombin inhibitors offer a potentially improved profile and possibly more effective alternative. Examples include recombinant hirudin or its derivative, hirulog, which affects both free and clot-bound thrombin activity. In the same way that heparin is an important addition to ASA treatment, these agents are better than ASA alone.[24,25] However, the improvements in outcome associated with the use of more selective thrombin inhibitors are small when directly compared to unfractionated heparin.[26] The effective dose is an issue still to be defined whereby the newer drugs may be shown to be more effective[27] but as yet this has not been established in large-scale clinical trials. It may be that a more appropriate comparison for the new thrombin inhibitors is not unfractionated heparin but low molecular weight heparin, yet no studies currently address this comparison in unstable angina.

Advances in platelet inhibition: supplements or alternatives to aspirin: ticlopidine, clopidogrel and IIb/IIIa antagonists

Platelet inhibition is essential in unstable angina management. Aspirin is the main agent used and is a proven effective therapy in all trials.[28] Notwithstanding this, greater levels of platelet inhibition can be achieved in a number of ways. The most widely-studied alternatives are the platelet ADP receptor blockers: ticlopidine and clopidogrel. Both of these drugs can be viewed as alternatives or supplemental therapy to ASA. Both have shown benefits when used as monotherapy or in combination with ASA in terms of clinical events, both in atherosclerotic stroke and in the management of occlusion after percutaneuous coronary revascularisation procedures (balloon angioplasty or stent placement).[29,30] Whether they are superior or equivalent to ASA as monotherapy has created some debate,[31] although combination treatment seems to be accepted as being more efficacious. Equally, some concern remains over the costs and toxicity of both these drugs, although particularly for clopidogrel, there appears to be good data from at least one large clinical trial that this agent is as safe as ASA.[32]

Great interest surrounds the use of the new intravenous or oral inhibitors of the glycoprotein IIb/IIIa receptor. As the final common pathway in platelet activation, this is a fundamental advance in the degree of inhibition of platelet aggregation which is possible. The agents under development range from monoclonal antibodies to non-peptides to be given as intravenous and oral agents, with variable pharmacokinetic and pharmacodynamic effects.[33] In unstable angina, published clinical trial experience is as yet limited; IIb/IIIa receptor antagonists appear to have promise in reducing the incidence of infarction in comparison to patients treated with aspirin.[34] While they have a distinct mode of action, unfortunately the major clinical trial published with a IIb/IIIa antagonist had a curiously low (28%) uptake of heparin/anti-thrombin therapy, which may overestimate the potential benefits. While they have created most interest in the management of complications following interventional coronary procedures (angioplasty and endovascular stent restenosis or occlusion) their use may be relevant in the interventional management of unstable angina (see below).

Conventional anti-ischaemic therapy

As with many areas of cardiac therapy, the role of 'conventional' treatments of unstable coronary syndromes, with vasodilating calcium antagonists, nitrates and beta blockade, have almost taken a back seat to interventional therapy. While there can be little doubt that these agents are effective symptomatically in chronic stable angina,[35] their impact on patient outcome in unstable disease is less well documented and evidence for reductions in cardiovascular events following an episode of unstable angina is remarkably absent.

Can aggressive lipid lowering be a sub-acute anti-ischaemic strategy

Consideration of lipid lowering (specifically LDL-cholesterol) as an anti-ischaemic strategy is not a new suggestion, and indeed predates the intervention trials with statins by several years. The dynamic nature of the unstable coronary plaque prior to abrupt closure is well established in a variety of cellular and experimental models, and is supported by a range of human data collected from coronary arterial specimens obtained pre- and post-mortem. While aggressive lipid lowering provides acute reductions in circulating LDL-cholesterol of the order of 30-60% with potent and long-lasting statin therapy, theoretically beneficial effects on plaque stability are obvious,[36] and are supported by a limited amount of clinical trial evidence looking at unstable angina as an end-

point of primary or secondary prevention in asymptomatic individuals.[37,38] Equally, primary prevention studies looking at ambulatory ST segment changes suggest that the emergence of benefit may occur in remarkably short time-scales of the order of weeks.[39] These are clearly relevant to the current management of unstable coronary disease, and large-scale studies of this effect are underway.[40] Logically in the acute phase, the magnitude of the effect on ischaemia might be expected to follow the size of the impact on serum lipids, favouring the use of more potent and long-lasting statins.

Thrombolysis and fibrinolysis in unstable angina

Thrombolysis has little use in unstable angina, having shown no clear evidence of benefit and some evidence of potential harm in the Thrombosis in Myocardial Infarction IIIB (TIMI) study.[41] This is an inappropriate therapy, particularly where direct interventional treatments are to be considered, as the likelihood of local coronary complications resultant from these are patently increased.

Pharmacological therapy:

- While effective in symptom control, benefits in terms of reduced mortality of incremental conventional anti-ischaemic therapy are largely assumed rather than proven in clinical trials.
- Aspirin and [some form of] anti-thrombin therapy are essential for all patients with unstable angina.
- Low molecular weight heparin is an acceptable alternative to unfractionated heparin, and may be modestly superior, but there is a significant overall cost issue.
- Alternative antiplatelet strategies may be useful in addition to aspirin but are probably not significantly better as monotherapy.
- Platelet receptor antagonism by monoclonal antibodies or non-peptide IIb/IIIa antagonists may be superior to aspirin but have yet to be convincingly tested in clinical trials.
- Aggressive lipid-lowering therapy may be active in the short to medium term.
- Thrombolysis is not effective, and may worsen outcomes during subsequent management.

ACUTE INTERVENTIONAL CORONARY MANAGEMENT

A variety of percutaneous revascularisation techniques have achieved an established role alongside bypass surgery in the management of symptomatic, yet stable, ischaemic heart disease.[42,43] These have also been studied in unstable patients alongside the improvements in 'medical' therapy. While in the former patient groups stability and elective management is the basis of treatment, in the latter the opposite is the case. While a chronic, symptomatic, usually severe stenosis is often responsible for chest pain in the stable patient, those lesions responsible for unstable angina need not produce severe stenosis, but they are frequently functionally unstable and prone to abrupt closure. This increases the dangers of abrupt closure during diagnostic arteriography, even prior to passage of a guide-wire across the lesion to facilitate interventional procedures. In controlled circumstances, the prospective VANQWISH study[44] did not see advantages in pursuing angioplasty-based revascularisation in unselected patients when compared

to an ischaemia-guided strategy. This does not suggest that urgent revascularisation is inappropriate; rather it supports the pivotal role of patient selection.

Controlled prospective trials of interventional management are as yet limited. A variety of sub-studies of larger trial databases suggest that there can be benefits in terms of reduced hospital stay and increased time to re-hospitalisation following interventional revascularisation. However, there may be a price to pay in terms of intra-procedural mortality and the continuing need for repetition of this revascularisation intervention. A reduction in re-stenosis is being actively pursued through adjuvant therapies. Ullrich Sigwart, the internationally renowned interventional cardiologist, candidly summed up the current state of the world literature on this subject at the 1997 Scientific Sessions of the American Heart Association as evidence of increased cost with no clinical benefit.[45] He stated clearly the urgent need for controlled studies using appropriate technology (endovascular stents) and clinical rather than angiographic endpoints. Most tertiary hospitals are committed to addressing these problems.

In the UK, the conduct of such high-risk interventional procedures has been developed with emergency coronary surgery as a backup. While the data describing the rate of emergency surgery is not complete, a 2% surgical intervention rate has been quoted by the appropriate subsection of the British Cardiac Society.[46] An acknowledged important aspect of this figure depends on the skills of the operators involved to enable them to acquire and retain competence. As endovascular stent technology and adjuvant treatment continue to evolve, management of suitable lesions may become considerably safer but not easier. The availability of such techniques may have reduced the need for emergency bypass procedures but, for the time being, accurate estimates are lacking.

In the management of unstable coronary disease as distinct from stable coronary lesions, the rapid evolution of techniques has made angioplasty/stent technology a moving target of assessment. It is clearly dependent on a combination of the operator, device and patient. There is no large-scale or firm evidence to compare intervention with either pharmacological treatment or 'complete' surgical revascularisation, although the experience of VANQWISH[44] and of the comparative studies in stable angina[40] suggest careful patient selection is the key to individual patient success.

THE 'DISTRICT' HOSPITAL (DGH) PERSPECTIVE

For the forseeable future, the care of the majority of patients with unstable angina will take place in general hospitals. Most patients admitted to hospital will be managed by general physicians with or without an interest in cardiology. In the relatively near future most, if not all, hospitals will have at least one physician with an interest in cardiology, and many larger district hospitals will have two. This should allow the management strategies to be agreed within the consultant body and any difficult cases to be transferred for specialist care and investigations.

As new ways of triaging patients emerge, the utilisation of chest pain services and of more experienced staff at an early stage after admission, or indeed making the decision to admit patients at all, should enable unstable coronary syndrome patients to pass more readily and quickly to CCU. Almost all acute UK hospitals now have a CCU which provides the correct environment for management, but it is worth re-emphasising that these patients are in some ways more in need of specialised monitoring than uncomplicated, haemodynamically-stable patients with established infarction. Accordingly, the routine transfer out of CCU should be biased to favour the admission of the patient with unstable angina. While troponin assays may have an increasingly distinguishing capability in immediate (emergency department) management decisions, their cost-effective introduction probably lies alongside a non-admission policy to

facilitate elective out-patient investigation of 'non-cardiac' chest pain. Widespread application of a troponin assay, in preference to more traditional markers such as CK-MB, should probably await definitive cost-benefit analyses.

As all CCU departments have on-line electrocardiography, upgrading this to provide continuous ST segment analysis is an important step in the triage of patients for current 'this admission' investigation, up to and including the decision whether and when to perform coronary arteriography. Patients with no evidence of electrical instability or symptoms might be electively assessed using an appropriate stress study. Patients with symptoms but with no electrical instability should be considered for an early stress study whilst in hospital. Patients with electrical instability without symptoms should be considered for angiography on the current admission.

Changing patterns of pharmacological management should make all units more receptive to updating their protocols of management as and when the majority view changes. ASA and anti-thrombotic therapy, along with optimised and maximal anti-ischaemic therapy tailored to individual cardiovascular risk, should be available for all. At present, however, unfractionated heparin combined with ASA should be used on merit. The potential uses for combination antiplatelet treatment (addition of ticlopidine or clopidogrel) await definitive outcome data. An oral IIb/IIIa antagonist may be the first agent to seriously threaten to replace ASA and a variety of prototype drugs being developed and tested. The evidence for aggressive lipid-lowering as a secondary prevention is so strong that a maximal reduction in circulating cholesterol (or LDL fraction) should be aimed for in all patients regardless of age or gender. There is little hard evidence to suggest that there is a floor to this effect, but much substantial evidence that the lower the better in individual cardiac patients.

Primary invasive management of unstable angina should be the subject of further investigational assessment in the tertiary centres. The benefits of a selectively aggressive management policy among unstable patients appear to outweigh an unselective policy and are logically (if not proven to be) more cost-effective. While this is untested to the required level at present, an unselective invasive management strategy is not a feasible policy at present outwith surgical centres with high volume and experienced invasive cardiologists. In the DGH setting, the process of passaging selected patients to interventional cardiology and cardiac surgery must be further refined based upon management guidelines from tertiary centres. Further data are still needed on the safety of purely diagnostic angiographic studies in unstable patients where transfer times, in the event of an sudden closure of a critical vessel, for example, may be substantial. The most logical division in the first instance would seem to be to allow electrically-stable patients (as defined by continous ST segment analysis) to be investigated in the DGH catheter laboratory. The level of sensitivity provided by continuous ST segment analysis is a critically important step in this process and should, therefore, also be the subject of future clinical outcomes research.

The management of unstable coronary syndromes, including angina, is entering the spotlight recently held by thrombolysis for myocardial infarction. Many exciting and applicable developments are currently underway in the management of these patients. They will greatly influence both the DGH and tertiary hospital management of this disease, and the changes will significantly increase standards of care. They will also result in a radical alteration in the relationship between peripheral and central hospital cardiac practice, where central hospitals primarily receive unstable patients for urgent catheter-based or surgical revascularisation, rather than address diagnostic issues or adjust medical management.

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