Non-interventional management of acute coronary syndromes

Ticagrelor shows promise compared with clopidogrel but the absolute added benefit is small

In the linked study, James and colleagues report a planned subgroup analysis of patients enrolled in the PLATElet inhibition and patient Outcomes (PLATO) trial, who at randomisation were initially allocated to a non-invasive treatment strategy. They compared cardiovascular outcomes and major bleeding in people treated with aspirin who were randomised to receive ticagrelor or clopidogrel.1

Interventional management is recommended for most patients with acute coronary syndromes, but a more conservative approach can be taken in certain subgroups. For example, in ST elevation myocardial infarction, thrombolytic treatment is an option for patients who present one to two hours after the onset of symptoms when primary percutaneous intervention is not immediately available.2

Conservative management is also an option in some low risk groups with non-ST elevation myocardial infarction and unstable angina if the risk of intervention exceeds the benefit.3 Patients unwilling to accept intervention or with prohibitive comorbidities add to the requirement for effective, stand alone medical strategies: the Myocardial Ischaemia National Audit Project for England and Wales found that in 2009-10 about 35% of patients with ST elevation myocardial infarction and 36.4% with non-ST elevation myocardial infarction did not have angiography during the initial hospital admission.4

Antiplatelet treatment with aspirin (inhibits platelet aggregation through inactivating cyclo-oxygenase) and clopidogrel (irreversibly blocks the ADP P2Y12 receptor on platelets) is central to the medical management of myocardial infarction. Prognosis is better with dual antiplatelet therapy than with aspirin alone, despite an increase in the risk of major bleeding.5 This has driven the search for more potent agents with a lower risk of bleeding, although this may seem futile given the link between platelet function and haemostasis. There are other reasons to look beyond clopidogrel for the management of acute coronary syndromes, however, not least its status as a prodrug that requires transformation into an active metabolite by cytochrome P-450 (CYP) enzymes for its antiplatelet effect. This requirement means that it has a delayed onset of action, which can be disadvantageous, and that platelet inhibition is less intense in carriers of reduced function CYP alleles (although this does not always reduce clinical effectiveness).6

Prasugrel and ticagrelor are newer agents that block the ADP P2Y12 receptor more potently than clopidogrel.7 Prasugrel, like clopidogrel, binds irreversibly to the receptor and is a prodrug that requires hepatic activation, but its onset of action is more rapid, and platelet inhibition is more prolonged and apparently unaffected by reduced function of the CYP alleles. In one trial of dual antiplatelet treatment in acute coronary syndromes, prasugrel significantly reduced the primary outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke compared with clopidogrel.8 Not unexpectedly, however, this was associated with a significantly greater risk of major, including fatal, bleeding. The National Institute for Health and Clinical Excellence has therefore recommended that prasugrel is used only in patients who need immediate primary percutaneous coronary intervention (taking advantage of its rapid onset of action) or in patients with diabetes who are at increased risk of adverse outcomes.9 Prasugrel is also indicated for patients with acute coronary syndromes caused by stent thrombosis while taking clopidogrel.

Ticagrelor differs from clopidogrel and prasugrel in that receptor binding is reversible, it is not a prodrug, and it has a shorter half life, so that it needs to be taken twice a day. In the original PLATO trial of dual antiplatelet treatment in acute coronary syndromes, ticagrelor significantly reduced the primary outcome of vascular death, non-fatal myocardial infarction, and non-fatal stroke compared with clopidogrel (absolute risk 9.8% v 11.7%; hazard ratio 0.84, 95% CI 0.77 to 0.92), presumably because of its greater antiplatelet activity.10

An electron micrograph of a coronary thrombosis

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Public health and preventing violence

Information obtained when treating victims could help reduce future violence

Interpersonal violence is a leading cause of death in adolescents and young adults worldwide.1 For every death caused by violence, scores of people have injuries that require urgent medical care, and in 2004 an estimated 16 million such cases received medical attention.2 In the linked study, Florence and colleagues evaluate whether sharing anonymised information obtained during the clinical care of victims with police and local government partners ining anonymised information obtained during the clinical study, Florence and colleagues evaluate whether sharng anonymised information obtained during the clinical study, Florence and colleagues evaluate whether sharing anonymised information obtained during the clinical care of victims with police and local government partners

Interestingly, James and colleagues found no higher risk of bleeding in their subgroup analysis of 5,216 (28%) PLATO recruits who were intended for non-invasive management at the time of admission.3 This is a particularly important subgroup that rarely receives attention from triallists, despite the substantial number of patients who continue to be managed conservatively. Although 2,183 patients (41.9%) in this subgroup analysis had coronary arteriography during the index admission, the intention to treat analysis confirmed a significant reduction in the primary end point (composite of cardiovascular death, myocardial infarction, and stroke) for ticagrelor compared with clopidogrel, which was almost the same as the reduction seen in the main trial. Again, however, it is the absence of a significant increase in the risk of bleeding that is important and seems to set ticagrelor apart from prasugrel, whether an invasive or conservative strategy is adopted in the management of acute coronary syndromes.

Has ticagrelor achieved the elusive goal of enhancing platelet inhibition and improving cardiovascular outcomes without increasing the risk of bleeding? The PLATO trial and the linked subgroup analysis in people who had non-invasive treatment certainly suggest so, although a convincing mechanism has yet to be presented. Nevertheless, with European regulatory approval already given and US approval expected shortly, ticagrelor already has a class 1 recommendation in the recent European revascularisation guideline for use in combination with aspirin for the invasive management of acute coronary syndromes,4 and similar recommendations are likely to follow soon for non-invasive management.

However, it is early days for ticagrelor, and some will wish to suspend final judgment, particularly as James and colleagues’ analysis found that the trend towards major bleeding, although not significant, was less with clopidogrel. Others will note the high rates of non-invasive management, particularly in patients with adverse risk characteristics who might have had most to gain from revascularisation. This might reflect real world practice, but it is a sobering fact that optimising access to invasive investigations is more likely to reduce mortality in patients with acute coronary syndromes than further refinement of existing antiplatelet strategies.5 The final verdict on ticagrelor must await the results of cost effectiveness and long term safety studies. If these are favourable they are likely to ensure a continuing role for ticagrelor in the non-invasive and invasive management of acute coronary syndromes.


REFERENCES
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A strong dose-response relationship exists between levels of violence and potentially modifiable factors

incident to the police. Thirdly, that by combining data from health services and the police, predictions of future violence can be improved. Fourthly, that when patterns of violence are accurately predicted, the frequency of future acts of violence can be reduced by tackling the underlying causes and risk factors.

The statistical predictability of violent incidents and injuries has been well established in developing and developed countries, where since the 1980s epidemiological methods have been applied to understand the magnitude, characteristics, consequences, and causes of violence. Crucially, these studies show strong dose-response associations between levels of violence and potentially modifiable factors such as economic inequality; accessibility to and misuse of alcohol and firearms; poor monitoring and parental supervision of children; and behavioural problems, such as impulsivity and hyperactivity.

Fewer studies have compared levels of violence shown by police recorded data versus data from health services, and most compare violence related deaths recorded in police statistics with those reported by mortuary based fatal injury surveillance systems. Such studies show that although in developed countries there is some under-ascertainment of homicides in police statistics, in developing countries the gap is larger and official police statistics substantially undercount the number of homicide victims seen in mortuaries (Shaw M, van Dijk J, Rhomberg W. Determining global crime and justice trends: an overview of results from the United Nations surveys of crime trends and operations of criminal justice systems. Unpublished background document prepared for the Expert Meeting on the World Crime and Justice report, 2004-2005, 26-28 June 2003, Turin, Italy). Such comparisons inform recommendations from the United Nations that to improve surveillance of violent deaths, data sharing between police, coroners, and other relevant services is essential.

By extending a similar line of reasoning to non-fatal cases of violent injury, Florence and colleagues’ findings on the extent to which police data under-ascertain violence related injuries in the UK is important for doctors, police, and public health experts in other developed countries. In developing countries where the availability of and access to medical care is less than in developed countries, local studies are urgently needed to explore the patterns of ascertainment by health services and the police.

The assumption that by combining health data and police data, violence can be more accurately predicted raises several questions. Are police recorded cases qualitatively similar to those seen by health services? When compared with findings from population based surveys, which dataset performs best? Studies are needed to answer these questions, and to quantify the predictive value added by combining sources. It can be assumed that the combination of police data and health service data more accurately predicts violence because it produces a more complete sample of all violence related injuries than either source alone. However, because some highly prevalent forms of violence (such as child maltreatment, intimate partner violence, sexual violence, and elder maltreatment) only infrequently result in injuries that require medical care, these forms of violence are best measured through population based surveys.

The prevention of interpersonal violence has been reasonably well established through outcome evaluation studies, including randomised control trials, with the strongest evidence available for programmes aimed at preventing youth violence and child maltreatment. However, most of these are studies of programmes that operate at the individual level and close relationship or family level, and almost all are from developed countries.

Fewer evaluations exist of potentially more effective and more cost effective societal and community level programmes, such as the Cardiff one. In light of its large effect on preventing violence, this model will hopefully be emulated by other cities in developing and developed countries, in each case with at least the same level of monitoring using health service and police records as was applied in the original study.

Despite the practical barriers to performing a randomised controlled trial of the intervention with the city as the unit of randomisation, it should be attempted. If subsequent randomised controlled trials or even less definitive experimental studies also find the significant reductions in violence shown in Cardiff, it would increase confidence in the value of this new tool to prevent violence.

Measles outbreak in Europe

Despite the current threat in Europe rates of infection are declining globally

Current outbreaks of measles in Europe are a reminder of the important risks of death and serious morbidity associated with measles. Between 2009 and 2010, cases of measles increased dramatically in Europe, with notifications increasing from 7175 to 30 367. In 2010 most reported cases were in Bulgaria (22 005), but there were also 5019 in France, 861 in Italy, 787 in Germany, 406 in Ireland, 733 in Austria, 528 in Norway, 443 in Denmark, 406 in Iceland, 292 952 in 2010, with rates of infection falling most in the African and Western Pacific regions. In 2010, 63.7% of the cases reported globally were from the Americas, 17.1% were from South East Asia, 14.7% were from the Western Pacific, and 3.6% were from the Eastern Mediterranean. Cases from Europe accounted for 0.9% and cases from the Americas accounted for less than 0.1% of those reported globally. Between 2000 and 2008 annual global mortality related to measles fell by 78%, from an estimated 733 000 to 164 000 deaths.

The low rates of measles in the American continent show what can be achieved. In the United States measles has been eradicated since the late 1990s (eradication is defined as an absence of endemic transmission and the US has seen an average of 56 cases a year from 2001 to 2008). Measles was eradicated in the rest of the American continent in 2002. The current 15 year high in US cases is largely accounted for by unvaccinated returning travellers who have become infected in Europe and South East Asia.

Measles is coming, but are we ready?

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Most people who have been infected in the current outbreak have never been vaccinated with MMR

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Response on bmj.com Measles is coming, but are we ready?

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in the UK among those who are now teenagers and young adults, has been shown to be based on discredited and even fraudulent research.\textsuperscript{11} Measles is highly infectious, with as many as 90\% of susceptible contacts becoming infected.\textsuperscript{9} The characteristic rash appears after seven to 21 days, and unvaccinated travellers infected abroad are likely to import and spread infection during the incubation period. Measles should be suspected in unvaccinated recent travellers with fever, coryza, conjunctivitis, and cough; notification and control measures should be based on suspicion, although laboratory confirmation is also needed.

Rates of measles seroconversion after vaccination are around 90\% after a single dose and 99\% after two doses.\textsuperscript{12} WHO recommends 95\% uptake of two doses of measles containing vaccine for elimination of the infection in a population, but pragmatically 90\% coverage of one dose is the current global minimum target.\textsuperscript{10} In non-endemic low transmission areas the first dose is ideally given soon after the first birthday (to avoid interference by maternal antibody and to maximise seroconversion) and the second dose before school entry, especially in the context of increased incidence of measles. However, MMR vaccination can be given before the first birthday, routinely at 9 months in high transmission, high mortality areas. In the case of travel to an endemic area it can be given as early as 6 months of age if immediate protection is required, with two further scheduled doses at the recommended ages.\textsuperscript{12} Given the age distribution of cases in the current European outbreak, we consider that catch-up programmes to immunise unprotected teenagers are essential to control and then eliminate measles in Europe.

### Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; RJR’s department has received small educational grants from GSK and Sanofi Pasteur to support an annual immunisation conference; no other relationships or activities that could appear to have influenced the submitted work.

### Provenance and peer review

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### The management of clinical commissioning groups

How they are held to account and governed matters; the government has a difficult balancing act

The government’s wish to be seen to avoiding top down direction in the specification of accountability and governance arrangements for the new general practitioner commissioning consortia, now to be called clinical commissioning groups, has backfired because the lack of detail has been seen as worrying vagueness. The Health Select Committee took a very critical view of this,\textsuperscript{4} and some Liberal Democrats have also highlighted that changes are needed.\textsuperscript{2, 5} Aspects of these arrangements therefore became an important focus for the Future Forum group, which has recently reported and to which the government has responded.\textsuperscript{4, 5}

There are several concerns. Firstly, will the groups have governance that is adequate for the large responsibilities and budgets they will hold? Secondly, will they be open and transparent, and ensure conflicts of interest are managed? Thirdly, how will they be held to account nationally and locally? There are also questions about how different constituencies would be represented in the work of the groups, in particular whether nurses, hospital consultant...
constructive external challenge mean that boards need a mix of different skills and independent members, usually in a non-executive capacity. Independent members could also have a useful role in protecting general practitioner board members from potential conflicts of interest. The government’s response to the Future Forum report recognises this and, in an important change, says that groups will have “at least two lay members, one with a lead role in championing patient and public involvement, the other with a lead role in overseeing key elements of governance such as audit, remuneration and managing conflicts of interest. One of the lay members will undertake either the role of Deputy Chair or Chair of the governing body.” This still leaves many unanswered questions—not least whether general practitioners will have non-executive roles.

The government, while not intending “to prescribe in detail the wider professional membership of the governing body,” also states that the governing body should have a nurse and a secondary care clinician; it is not specified whether these are to be executive or non-executive roles. To prevent a conflict of interest, these people cannot be employees of a local provider. Exactly what value this will bring is not clear. There are also some practical problems about where these people will come from, and if they are not connected in some way to the area that is served why they would want to be involved. The forum made other recommendations for providing advice to groups and proposed a clinical senate. The government has adopted this, and the senate will give advice that consortia will be expected to follow. The senate will also include public health specialists, and this deals with an anxiety about the provision of population health advice. How these will work or avoid a problem with conflicts of interest, which are such a concern to government, is yet to be explained. These new proposed structures also create a complexity that is potentially costly to administer and opaque to local populations.

Some people proposed that these boards should have representatives from local government, acute hospitals, and other interested parties. This misunderstands the role of independent board members who—although they can be an important bridge to the public, councils, and others with an interest—have a primary responsibility to ensure that the organisation is well governed, has a coherent strategy, and that its management is challenged. Incorporating a representative role would confuse this function and be likely to impair the effectiveness of the board. Questions about how the consortia will be held to account have also caused concern. Some of the mechanisms initially proposed look underpowered, whereas—as Walshe and Ham note—others, particularly those held by the NHS Commissioning Board, look potentially draconian. The NHS Commissioning Board will hold commissioning consortia to account for the delivery of an outcomes framework and the application of the commissioning frameworks. Although intervention is possible in the event of failure, how the system will promote improvement or deal with “coasting” consortia is still not clear. Whether the publication of performance data and the use of a relatively limited incentive will be sufficient seems doubtful. It now seems that there will be a continuing process of holding consortia to account, and previous experience in the NHS suggests that even though it will be intended as “light touch” it will tend to expand and become more demanding unless deliberate steps are taken to avoid this.

The health and wellbeing boards and the local scrutiny arrangements may help fill this gap in national accountability. These new pieces of machinery are potentially very important for developing plans and local priorities. They could have a positive impact, but this will depend on the nature of relationships locally.

The changes proposed by the Future Forum are helpful and deal with several genuine concerns. Whether the government’s response is as helpful is less clear.

What is striking is that one of the aims of the reforms was to reduce bureaucracy, but at the end of this process, although 151 primary care trusts and 10 strategic health authorities will have been abolished, there will be a very large commissioning quango with regional branches, at least 250 new consortia, 152 new health and wellbeing boards, and an unknown number of clinical senates. When, as is inevitable, clinical commissioning groups make difficult rationing decisions it will be too easy to shift the blame to “the bureaucracy,” and the cycle of reorganisation could start again. If these reforms had focused on groups of clinicians working together to redesign care, with the payment and holding to account functions being done at a more aggregated level, which is increasingly the case in other European countries, then the need to construct such complex machinery to prevent conflicts of interest might have been avoided.

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