

reimbursement for such an approach is not universal. The results of IN-TIME suggest that such redesign could be worthwhile, by improving patient outcome with little additional work. But many questions remain: remote monitoring shows much promise but how such services should be set up, and with which technologies, is still unclear.

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## Risk and decision making in patients with hypertension

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In *The Lancet*, the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) report an individual patient data meta-analysis of trials that randomly assigned patients to blood pressure-lowering drugs or placebo, or more intensive or less intensive blood pressure-lowering strategies.<sup>1</sup> The expected, albeit important, conclusion of the study is that blood pressure-lowering drugs provide a similar relative benefit across different strata of predicted cardiovascular risk: in an analysis of 51 917 participants in 11 trials, blood pressure-lowering treatment reduced the relative risk of events in patients in four groups of increasing estimated baseline cardiovascular risk by 18% (95% CI 7–27), 15% (4–25), 13% (2–22), and 15% (5–24), respectively. Hence, by definition, the absolute benefit of treatment would increase with the baseline risk, and treatment of 1000 patients in each group for 5 years should prevent 14 (95% CI 8–21), 20 (8–31), 24 (8–40), and 38 (16–61) cardiovascular events, respectively. The number-needed-to-treat to prevent an event would decrease accordingly.

This study is reminiscent of a landmark analysis undertaken by the Cholesterol Treatment Trialists

that showed the absolute benefit of cholesterol reduction with statin treatment to be proportional to the baseline absolute cardiovascular risk.<sup>2</sup> The BPLTTC analysis is timely and important because its findings could affect future revisions of hypertension guidelines that seem to be reluctant to consider total cardiovascular risk, instead of blood pressure alone, as the main driving force to guide initiation of treatment.<sup>3–5</sup>

Understanding the methods of the BPLTTC study is not purely academic, but pivotal to realise the extent to which the findings are generalisable.<sup>6</sup> The authors used the placebo groups of ten trials with available time-to-event data to develop risk prediction models for six prespecified outcomes. A parsimonious set of covariables, with the notable exception of blood lipids, was used to balance model fit with the availability of risk factor data. Subsequently, they applied the equations to all trial participants and ranked them by estimated absolute 5-year risk of outcome events. 5-year risks, rather than more conventional 10-year risks, were estimated because 5 years was closer to the actual median follow-up of 4 years. Thereafter, considering

only the patients with an event, they defined three cutoff points of estimated risk that would divide the individuals into four equally sized groups. Finally, they applied these cutoff points to the overall trial population to define the four main risk strata. This approach is a laudable attempt to maximise the power and precision of the estimated treatment effects in each of the four risk strata by creating four risk groups with the same number of outcome events.

However, to understand for which purpose the risk prediction models were developed and how their validation was done is crucial. This aspect of prediction modelling is vital, because it allows researchers to establish whether a model is transportable to similar patients in other settings. The concept is often referred to as generalisability, and a model that passes such a test is said to have been validated.<sup>7</sup> For the proof-of-principle shown in this study, internal validation might be adequate, and important measures of that—the observed versus expected event rates—are graphically presented in the study's appendix. However, although the authors are not explicitly promoting these equations for general use, the absence of external validation somewhat limits the generalisability of the findings. Risk prediction models are increasingly used in clinical decision making, and proposed models need to provide accurate and validated (internally and externally) estimates of probabilities of outcome events in the targeted patients.<sup>8</sup>

This leaves two open questions: to what extent are the patients in these studies' placebo groups really representative of patients with hypertension encountered in clinical practice? And can we be sufficiently confident about the accuracy of the prediction equations in a contemporary clinical context? With the exception of two studies that enrolled a well-defined hypertensive population of elderly patients with systolic blood pressure of greater than 160 mm Hg,<sup>8,9</sup> most studies enrolled patients with a wide range of blood pressures who also had several concomitant risk factors including diabetes, raised blood lipids, proteinuria, history of stroke, and coronary artery disease. Even more important, only a small proportion of patients had uncomplicated mild hypertension.

Another issue questioning the accuracy of the risk equations is that most studies were published at

Recommendation in patients with grade I hypertension	
ESH/ESC <sup>11</sup>	BP-lowering drugs recommended when total cardiovascular risk is high because of organ damage, diabetes, cardiovascular disease, or kidney disease
JNC 8 <sup>4</sup>	BP-lowering drugs recommended to lower BP <140 mm Hg systolic and 90 mm Hg diastolic in patients aged <60 years, and <150 mm Hg systolic and 90 mm Hg diastolic in patients aged >60 years
CHEP <sup>5</sup>	BP-lowering drugs strongly considered in the presence of macrovascular target organ damage
ASH/ISH <sup>12</sup>	BP-lowering drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle measures have not been effective
NICE <sup>3</sup>	Offer antihypertensive drug treatment to people younger than 80 years with stage 1 hypertension and who have one or more of the following: target organ damage, established cardiovascular disease, renal disease, diabetes, or 10-year cardiovascular risk equivalent $\geq 20\%$

ESH=European Society of Hypertension. ESC=European Society of Cardiology. BP=blood pressure. JNC 8=Joint National Committee 8. CHEP=Canadian Hypertension Education Program. ASH=American Society of Hypertension. ISH=International Society of Hypertension. NICE=National Institute for Health and Clinical Excellence.

**Table: Position of major guidelines on antihypertensive treatment in patients with grade I hypertension**

least a decade ago, and done in the years before that. Hence, patients randomly assigned to placebo in these trials might have been exposed to less intensive management of risk factors—eg, lower use of statins—compared with current standards. Statins might have been one of the reasons why trandolapril did not reduce cardiovascular risk in the PEACE trial,<sup>10</sup> despite efficacy having been shown in previous placebo-controlled trials with angiotensin-converting enzyme inhibitors.

Beyond the elegant demonstration of a proof-of-concept, several important aspects need to be further investigated. First, the accuracy and external validity of the prediction models should be tested in contemporary cohorts of patients. Second, whether treatment decisions mainly based on total cardiovascular risk outperform decisions mostly based on blood pressure should be clarified. Patients at relatively low risk of cardiovascular events, such as younger patients with hypertension or those with low phenotypic expression of risk factors, should not be denied treatment with the argument that the expected absolute benefit is small.

Indeed, the discrepancies between some hypertension guidelines in the approach to patients with grade I hypertension (blood pressure 140–159 mm Hg systolic or 90–99 mm Hg diastolic)

do not seem to be substantial (table). Because all guidelines recommend prompt initiation of drug treatment in patients with hypertension stage II or III, estimates of total cardiovascular risk in this setting might not have a major effect on therapeutic decisions, but rather on the expectations of benefit. In patients with hypertension stage I, with the notable exception of the Joint National Committee 8, the other guidelines take cardiovascular risk estimates into some account, by recommending the initiation of drug treatment when the risk is increased generally on the basis of target organ damage or established cardiovascular disease. Future studies should focus on stage I hypertension and clarify what is the most accurate and cost-effective approach to stratify cardiovascular risk and to estimate the expected benefit of treatment in these patients.

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## Heparin monotherapy for percutaneous coronary intervention?

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The efficacy and safety of percutaneous coronary intervention (PCI) has been substantially enhanced by refinements in antithrombotic treatments. Ischaemic complications were reduced by as much as 50% with addition of platelet glycoprotein IIb/IIIa inhibitors (GPIs) to early regimens of aspirin and heparin.<sup>1,2</sup> However, use of these potent platelet inhibitors was accompanied by increased risk of haemorrhagic complications, which are associated with increased mortality, morbidity, and costs.<sup>3,4</sup> Development of antithrombotic drugs therefore focused on reducing risks of haemorrhagic events while maintaining protection against ischaemic complications. In several trials in patients undergoing PCI, substitution of the direct thrombin inhibitor bivalirudin for the combination of heparin and a GPI consistently reduced the incidence of major bleeding by about 40%.<sup>5–7</sup>

Although occurrence of the composite ischaemic endpoints of those trials was not significantly increased by bivalirudin, there seemed to be more frequent periprocedural myocardial infarctions in several studies and rates of acute stent thrombosis were significantly higher with bivalirudin than with heparin in patients with ST-elevation myocardial infarction (STEMI). However, long-term mortality was not increased with bivalirudin and this drug largely supplanted the combination of heparin plus a GPI during PCI.

Advances in interventional practices have the potential to alter the balance between bleeding and ischaemic risks. Ticagrelor and prasugrel—potent and rapidly acting inhibitors of the platelet ADP receptor—reduce ischaemic events when used instead of clopidogrel in patients with acute