A New Approach to Residual Risk in Treated Hypertension—3P Screening

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The treatment of primary hypertension has been one of the major success stories of clinical medicine over the last 50 years. However, there is still room for further improvement because it is now appreciated that optimally treated hypertensives still have considerable residual cardiovascular (CV) risk. A recent article showed that even after correcting for systolic blood pressure (BP), a treated hypertensive patient has a 50% increased risk of any CV event.1 Intriguingly this is not the case for lipid-lowering therapy, which is able to negate all of the increased risk caused by hyperlipidemia. When the total CV risk in treated hypertension was broken down further, the increased risk of coronary disease was 46%, for stroke it was 75%, and for CV death it was 62%. Numerous other studies have found the same increased residual CV risk in treated hypertensives.2-7

Case Report

A 65-year-old man was diagnosed with primary hypertension 15 years ago at the age of 50 years. There were no noteworthy features about this man and his family history was unremarkable. He was an ex-smoker (only 4 years) with a body mass index of 24, who ingested 10 U of alcohol per week. His hypertension was well controlled on a combination of lisinopril (20 mg) and amlodipine (5 mg). His office BPs were 130/78 mm Hg. His home BPs, recorded by himself, averaged 116/78 mm Hg. His lipid profile was normal but he was commenced on a statin 3 years ago (atorvastatin 10 mg) in view of the earlier ASCOT/LLA (Anglo Scandinavian Cardiac Outcomes Trial/Lipid Lowering Arm) study results.

Despite the above, he was admitted to hospital with an anterior ST-segment–elevation myocardial infarction (STEMI), which was appropriately treated with angioplasty and all other routine therapy, including the addition in the long term of aspirin, a β-blocker, and an increase in atorvastatin dose (to 80 mg). His most recent investigation showed a reduced left ventricular (LV) ejection fraction of 42%.

Having been told that his BP was well controlled, he was puzzled as to why he had developed an overt CV event (an STEMI) which now put him at risk of future heart failure and why his physicians had not been able to either better predict the STEMI or better still prevent it occurring. His case illustrates well residual risk in treated hypertension.

Residual Risk in Treated Hypertension

A knee-jerk response to improve the situation with regard to residual risk in hypertension would be to target a lower achieved BP than is currently advised. However, attempts to do this have generally disappointed (ie, efforts to achieve a lower than current target BP have not delivered extra benefit and adverse effects have been prominent).8 We obviously need a smarter approach to this problem.9

To address residual risk, the first question we need to ask is what (silent) CV abnormalities are actually present in optimally treated hypertensives that may be causing the residual risk. Nadir et al10 recently showed that 34% of optimally treated hypertensives have silent, asymptomatic cardiac abnormalities. LV hypertrophy (LVH) was the most prevalent (29%) followed by LV diastolic dysfunction (LVDD; 21%), left atrial enlargement (LAE; 15%), LV systolic dysfunction (LVSD; 6%), and silent myocardial ischemia (SMI; 6%). In this study, SMI was assessed by dobutamine echocardiography which has a sensitivity of 72% to 86% and a specificity of 77% to 95%.11 The other abnormalities were assessed by echocardiography which is the current gold standard for LVH, LVSD, LVDD, and LAE. Crucially these abnormalities were often multiple in individual patients. Of those with cardiac abnormalities, 1 abnormality was seen in 29%, 2 in another 31%, 3 in another 29%, and ≥4 in 10%. Thus, 13% of all treated hypertensives have ≥3 silent cardiac abnormalities which may well explain a lot of the residual risk of treated hypertensives.

This above information may also explain why a new lower target BP for all is not an effective way to tackle the problem of residual risk in treated hypertension. If residual risk is caused by a combination of silent LVH, LVDD, LAE, LVSD, or SMI, then most of these will not be cured by a further reduction in BP per se. For example, amlodipine reduces BP but is known to be ineffective in LVSD.12 Angiotensin receptor blockers reduce BP but are known to be ineffective in LVDD according to the largest study.11 Thiazides would not help in established SMI, although they reduce BP. The only situation where a lower target BP may well help is in LVH, as it...
has been shown to further regress LVH.\textsuperscript{14} This suggests that a much more targeted approach is needed where the precise cause of the residual risk is identified and treated specifically.

The next key question is whether it would be worth identifying the 34% of treated hypertensives who are harboring the above silent cardiac abnormalities (and if so, how). To answer the second question first, identifying LVH, LVDD, LAE, and LVSD would normally require echocardiography in all treated hypertensives, and there is general agreement that this would not be cost effective. Furthermore, identifying SMI would require a different test, which would involve either a stress test or a radiation exposure (computerized tomography coronary calcium); these latter tests would both be daunting as routine tests, especially considering that SMI is only present in 6% of such asymptomatic individuals. However, recent data from our group suggest that B-type natriuretic peptide (BNP) (\pm high sensitivity troponin) screening would be a cost-efficient way to identify which treated hypertensive patient is likely to have any of LVH, LVDD, LAE, LVSD, or SMI.\textsuperscript{10} The c-statistic was 0.78 for this (0.81 for BNP+hs troponin). The area under curve for the receiver operating curve for hs troponin on its own was lower (0.70). The sensitivity and specificity of BNP varied at different BNP levels, but at 10 pg/mL, it was 85% and 51%; maximizing sensitivity to avoid false negatives is best where a more definitive test follows (as here). The sensitivity and specificity of combining BNP (15 pg/mL) and hs cTnT (5-9 ng/L) was 87% and 65%. Of particular importance was the fact that BNP accurately identified the worst cases (ie, BNP accurately identified \textgreater 93% of those with \textgreater=2 cardiac abnormalities or with LVSD on its own or with SMI on its own).

Many earlier studies in various different populations had already shown that BNP could identify 1 or 2 isolated abnormalities like LVH, LAE, LV dysfunction, or silent ischemia. However, the importance of the new study described above is that all forms of cardiac abnormalities were looked for in the 1 study.\textsuperscript{10} This is very important because, patients harboring forms of cardiac abnormalities not assessed in earlier studies will mistakenly appear as false positives for BNP; this will not occur if the search for cardiac abnormalities is comprehensive, as in this recent study.\textsuperscript{10} Of course, BNP levels can be altered by renal dysfunction and obesity and future research should address the effect of these complicating factors and whether BNP testing can be applied to these subgroups (and if so, at what levels).

How do we know that, if we used BNP to identify those with LVH, LVDD, LAE, LVSD, or SMI, we would be identifying those at the highest risk? There are 2 strong indicators that this is the case. First, Tsang et al\textsuperscript{15} showed that each of LVH, LVDD, LAE, and LVSD independently increases CV risk by \textgreater=40%, whereas SMI is well recognized as a cause of sudden cardiac death in apparently healthy individuals.\textsuperscript{16} Second, Nadir et al\textsuperscript{10} showed that those with any of LVH, LVDD, LAE, LVSD, and SMI have an elevated level of BNP, whereas Paget et al\textsuperscript{17} showed that a high N-terminal proBNP independently increased the risk of total mortality 3-fold in treated hypertensives. Overall, therefore, Paget et al\textsuperscript{17} clearly indicate that N-terminal proBNP can be used to identify those with the most residual risk, whereas Nadir et al\textsuperscript{10} show what known cardiac culprits are present in those with a high BNP (incidentally, BNP and N-terminal proBNP are usually virtually interchangeable in their diagnostic roles).

Therefore, it is reasonable to presume that BNP (\pm hs troponin) screening could identify those treated hypertensives who are harboring the most residual risk and who are harboring the kind of silent cardiac abnormalities which are known to increase CV events/deaths. The next key question is whether there are treatments for those silent cardiac abnormalities that, if instituted, would prevent CV events/deaths. There are indeed many highly promising options, although none are rigorously proven therapies for this precise group of patients. However, an additional key point is that each different underlying cardiac abnormality needs a different treatment (Figure). This means that current primary prevention in hypertension may be enhanced by a personalized medicine approach against the precise cardiac abnormality seen in each individual after BNP-guided phenotyping.

The potential personalized therapies are as follows. If silent ischemia is found, additional therapies which are not used routinely in all hypertensives are \β-blockade, aspirin (and statins). \β-Blockers have been relegated to fourth line antihypertensives. Guidelines are mostly fairly negative on the use

![BNP Guided Phenotyping followed by Personalised Therapy (3P Screening) in Treated Hypertension](https://hyper.ahajournals.org/)

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**Figure.** B-type natriuretic peptide (BNP)-guided phenotyping followed by personalized therapy (3P screening) in treated hypertension. BP indicates blood pressure; CABG, coronary artery bypass graft; LAE, left atrial enlargement; LVDD, left ventricular diastolic dysfunction; LVH, LV hypertrophy; and LVSD, LV systolic dysfunction.
of aspirin in primary prevention. Statins are used only selectively. One study did suggest that an anti-ischemic regime could reduce events by 80% in silent ischemia.\textsuperscript{18} As to other treatments for SM (coronary angioplasty and revascularization), 2 studies in silent ischemia have produced impressive results.\textsuperscript{19,20} If, on the contrary, echo LVH is found in a normotensive patient, new treatments could be allopurinol, copper chelation, extra BP reduction, or aldosterone antagonists as they are all effective at regressing LVH.\textsuperscript{14,21,22} If LVSD is found, the addition of β-blockers and aldosterone antagonists (to angiotensin-converting enzyme inhibitors) should markedly reduce risk, possibly by 40% according to the trials in early heart failure.\textsuperscript{2,3} It also seems sensible to try to detect all the independently harmful cardiac abnormalities rather than just those known to be currently treatable because new treatments are bound to be developed in the near future. For example, the TOPCAT (Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist) study might soon endorse aldosterone blockade for LVDD. LA dilatation predicts atrial fibrillation, which can predate strokes and sudden deaths; in the future, we might use aldosterone blockade to offload the heart and so prevent atrial fibrillation developing, as occurred in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study.\textsuperscript{24}

Thus, the best approach to improve primary prevention might be if each treated hypertensive was screened with BNP+high-sensitivity troponin T (hsTnT) and then was selectively phenotyped so that a personalized medicine approach (as described above) could supplement current primary prevention of those patients. Until now, primary prevention has hitherto focused on reducing longstanding risk factors like BP and cholesterol, but rather ignores whether an individual patient has already developed a silent cardiac abnormality that is not seen on the ECG. This is because the costs involved in phenotyping all treated hypertensives would make it prohibitive but prescreening with a biomarker that identifies those individuals most likely to be harboring silent cardiac target organ damage is a new option. Thus, individuals with high biomarker (BNP) levels could be selected for cardiac phenotyping and only those who are positive in both the biomarker test and the phenotyping would then be given personalized medicine against the abnormalities identified by phenotyping (Figure). This could be called 3P screening of treated hypertensives with a view to reducing their current 50% increased residual risk.

It is worth commenting on other potential ways to personalize risk prediction in treated patients. Obviously, composite risk factor predictors like Framingham have been devised for use in untreated patients. However, these risk scores struggle when it comes to estimating risk in treated patients. Indeed, 3 such risk scores performed poorly in Nadir et al\textsuperscript{10} when it comes to their being able to identify silent heart disease. One risk score suggests adding 20 mm Hg to the actual BP but there is little evidence base for knowing whether this is the correct figure or not. Indeed, in Paget et al,\textsuperscript{17} treated systolic BP did not independently predict mortality. Other potential ways of personalizing risk are to use micro albuminuria, creatinine/estimated glomerular filtration rate, and the ECG. Intriguingly, none of them performed well in Nadir et al\textsuperscript{10} at identifying silent heart disease, where the c-statistic for BNP/hsTnT was =0.2 higher than any risk score or micro albuminuria, or estimated glomerular filtration rate or any ECG abnormality or uric acid. Somewhat surprisingly in Paget et al,\textsuperscript{17} neither creatinine nor Sokolov ECG criteria significantly predicted mortality in treated hypertensives. Another possibility is to image peripheral arteries such as using carotid intima-media thickness or pulse wave velocity. Although they are independent predictors, they do not seem to have the high level of accuracy that would be needed for such technically demanding (and costly) tests to become screening tests. Intriguingly, vascular dysfunction does increase BNP and hence BNP may reflect vascular dysfunction to some extent.\textsuperscript{23} Of course, in the future, genomic analysis may become a good way to personalize risk prediction. There are other known risk factors but they are not easily quantifiable on an individual basis (eg, air pollution, passive smoking, social deprivation, and ex-smoking). Efforts to try to quantify such factors may prove useful in the future.

What is now being proposed is similar to cancer screening (ie, a simple screening test followed by selective more detailed tissue phenotyping). BNP+hsTnT performs just as well as most cancer screening tests. In fact it is ironic that screening programs have been developed to identify early target organ damage in cancer but not yet in cardiology. This is despite the fact that sudden cardiac death occurs not infrequently in the presymptomatic stage of heart disease.\textsuperscript{16} In fact, BNP screening might be better than cancer screening because 1 screening test (BNP) could identify 5 different forms of cardiac disease, whereas each cancer needs a different screening test. Future research should assess how often BNP testing needs to be repeated.

It is worth noting that in the literature, novel plasma biomarkers (like BNP) on their own have only modestly improved c-statistics for CV risk prediction over traditional risk factor scores.\textsuperscript{26,27} This is probably because the biomarker has a 40% false-positive rate that dilutes the prognostic value of the biomarker when used on its own.\textsuperscript{10} This new approach (3P screening) is very different from using BNP on its own in 2 ways. First, the patients who would be regarded as being at high risk by this new approach would have to fail both a biomarker test and specific investigations for cardiac target organ damage, each of which inflates risk independently.\textsuperscript{15,17} Second, 3P screening is not using the biomarker to enhance current risk scores per se (as much other research is doing) but rather takes the alternative approach of using the biomarker to identify which patients have already developed silent cardiac abnormalities (irrespective of which risk factors or genes may have caused them in the first place).

It is obviously important to consider the possible cost effectiveness of BNP screening followed by targeted phenotyping. It has been estimated that each life saved would cost ≈£3500 per year.\textsuperscript{10} This analysis only addresses total deaths and not the many nonfatal CV events and hospitalizations that 3P screening is also likely to reduce.

As mentioned above, BNP and troponin are particularly good at identifying the worst cases with >1 form of silent cardiac target organ damage. What this means is that each country could decide to set whatever level of cost it can afford to save each life. A high biomarker cutoff will at relatively low cost
identify the more serious cases, although clearly not all cases. However, richer countries could set a low biomarker cutoff level to save more lives, albeit at a greater cost per life saved.

Returning to the original case presentation, it is quite possible that before his STEMI, he had SMI for some time and that his BNP and its hsTnT would have been in the upper tertile of the BNP and hsTnT range. If so, after BNP screening, phenotyping might have detected the SMI which would be followed by the addition of aspirin and a β-blocker (and possibly with an increase in his atorvastatin dose) to his regime. How effective this might be in preventing his STEMI is unknown, but Erne et al.\(^\text{18}\) suggest very effective. His future risk is much greater now that he has a massive left ventricular ejection fraction as a result of his STEMI, whereas if 3P screening could have prevented his STEMI in the first place, his overall risk would be much reduced from its current level.

**Conclusion**

In summary, what is presented here for the first time is a new 3-stage personalized medicine approach to enhance current primary prevention in treated hypertensives and to reduce their considerable residual risk. It involves BNP (±hsTnT)-targeted cardiac phenotyping followed by a personalized medicine approach toward the cardiac abnormalities identified (3P screening). Clearly, large studies will be needed to see whether 3P screening really can reduce the current 50% increased CV risk in treated hypertensives and do so in a cost-effective way. If it did, this might one day elevate target organ screening in treated hypertensives into the same position as screening for certain cancers achieved long ago.

**Disclosures**

A.D. Struthers has been consultant to companies developing aldosterone-modulating drugs. He has a patent for xanthine oxidase inhibitors to treat angina.

**References**


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