The treatment of essential hypertension has improved dramatically during the past 50 years. However, even optimally treated hypertensives still have considerable residual cardiovascular risk (see below), and this residual risk exerts a huge impact overall because essential hypertension is such a common disease.

Why Residual Risk Needs Addressing
With regard to residual risk, an optimally treated hypertensive patient still has a 50% increased risk of a cardiovascular event even after correcting for systolic blood pressure, that is, a treated hypertensive is at 50% greater cardiovascular risk than an untreated normotensive with the same systolic BP.1 When the cardiovascular risk in treated hypertension is broken down further, the increased risk of stroke, coronary disease, and cardiovascular death are 75%, 46%, and 62%, respectively. Many other studies have found the same increased residual cardiovascular risk in treated hypertension.2–7 Intriguingly, the absolute risk reduction when BP is reduced and yet the higher also is the residual risk.8 Whatever the cause of this residual risk in hypertension, we ought to strive to find novel therapeutic strategies against it because this extra residual risk (50%) applies to >50% of all individuals aged ≥60 years in a population (ie, all the hypertensives). In other words, the scale of this problem is such that reducing residual risk, even modestly, could markedly reduce cardiovascular events/mortality overall and, thereby have an enormous impact on a population’s health and healthcare costs.

The most obvious strategy that has been attempted to reduce residual risk was to try setting a lower target BP than the current one. However, attempts to do this have been disappointing. The best example of this is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.9 We therefore need a better strategy to tackle this problem than merely using untargeted approaches, such as lowering target BP levels for all.

Identifying the Cause of Residual Risk
Therefore, to reverse the problem of residual risk in a new way, we need fresh thinking. We need to first consider what the underlying potentially treatable (silent) cardiac abnormalities are in those with the most residual risk. This first requires a way of identifying those at most residual risk. That can be done by identifying those with a high biomarker like B-type natriuretic peptide (BNP or N-terminal proBNP [NT-proBNP], which is really equivalent to BNP). Paget et al.10 showed that a top tertile level of NT-proBNP independently identified treated hypertensives, who had a 3-fold increase in total mortality during the subsequent years and this was after correction for 10 other traditional cardiovascular risk factors. This was confirmed by Welsh et al11 using data from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). They showed that NT-proBNP predicted future cardiovascular disease independently of achieved BP and with an odds ratio per SD increase in log NT BNP of 1.24 (confidence interval, 1.06–1.45; P=0.007). In the amlodipine limb of the study, those who achieved an NT-proBNP level below median (61 pg/mL) had 42% less future cardiovascular disease (OR, 0.58; confidence interval, 0.37–0.91). In the study by Welsh et al, the addition of NT-proBNP to all classical risk factors led to a net reclassification index of 23% (P<0.0001). As would be expected, the use of β-blockers in the other limb of the ASCOT confounded their BNP results because β-blockers independently increase BNP because the extra diastolic time induced by β-blockers increase diastolic filling/stretch and hence contaminate BNP levels in that subgroup. The articles by Paget et al10 and Welsh et al11 excluded other clinically identifiable causes for the elevated BNP, such as renal dysfunction and atrial fibrillation (AF). In fact, it is hardly surprising that BNP is an excellent independent predictor of cardiovascular events in treated hypertensives because such a strong independent link between BNP and cardiovascular prognosis has been seen consistently in all populations ever examined. In fact the hazard ratios are similar (2.5–3.5) in all populations as were seen in the study by Paget et al.10,12 BNP is therefore a way of stratifying treated hypertensives so that personalized medicine can be focused on those with high BNP/high risk to reduce their residual risk.

In summary, BNP or rather NT-proBNP (in the absence of β-blockers) can identify those treated hypertensives with the most residual risk. If we establish what silent cardiac abnormalities actually exist in such high BNP/high-risk individuals,
then we should be identifying the silent cardiac abnormalities causing the residual risk in treated hypertension.

Nadir et al. recently found that optimally treated hypertensives with a high BNP had a marked excess of silent myocardial ischemia, left ventricular systolic dysfunction (LVSD), LV hypertrophy (LVH), and left atrial enlargement (LAE). The average BP of 120/72 mm Hg and 55% of them had >1 abnormality. This was despite a treated hypertension being highly accurate (c-statistic, 0.78: in males, 0.81) in identifying all these silent cardiac abnormalities in treated hypertensives. In fact, one third of all optimally treated hypertensives had at least 1 form of silent heart disease and two thirds of them had >1 abnormality. This was despite a treated average BP of 120/72 mm Hg and 55% of them taking a statin. Some further confirmation that these cardiac abnormalities are likely to be the cause of the residual risk in treated hypertensives is desirable and comes from 2 other sources. First, silent ischemia is well known to increase the risk of a coronary event (by 21-fold according to Rutter et al.). Second, Tsang et al. have already shown that asymptomatic LVH, LVSD, and LAE strongly predict cardiovascular events, even when all are asymptomatic, for example, the increased independent risk because of LVSD, LVH, and LAE was 122%, 57%, and 42%, respectively. The Framingham study had already showed much the same, for example, in Framingham, asymptomatic LVH triples the risk of sudden cardiac death. Therefore, it seems highly probable that the residual risk in optimally treated hypertension is to a large part because of a combination of silent ischemia, silent LVSD, silent LVH, and silent LAE, although the evidence loop does lack a final definitive study showing that hypertensives who have cardiovascular events had these particular cardiac abnormalities (and a high BNP) earlier on.

**Treatment of Residual Risk**

If we can use BNP to identify treated hypertensives who are at high residual risk because of a combination of silent ischemia, LVSD, LVH, and LAE, what therapeutic options could we use to treat these 4 abnormalities and so reduce their cardiovascular events? Although these 4 cardiac abnormalities are diverse, 1 treatment in particular stands out as having a reasonable chance of being efficacious in all of them (Table). That intervention is β-blockers. Nowadays, β-blockers are at best a fourth line option for hypertension and hence they are seldom used for hypertension in the absence of any other overt symptomatic cardiovascular disease, that is, most hypertensives needing only primary prevention reach target BP on angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), calcium antagonists, and thiazides. Even if a fourth drug is needed in hypertension, it is often either spironolactone or doxazosin especially the former as it reduces BP more in resistant hypertension (although the PATHWAY 2 [Prevention and Treatment of Resistant Hypertension With Algorithm Guided Therapy] study is examining this). Our hypothesis is that adding a β-blocker to high BNP hypertensives already treated to target BP with either an ACEI/ARB, calcium antagonist or a thiazide might reduce residual risk. It is worth noting that this option of adding a β-blocker to a patient already on an ACEI/ARB and other antihypertensives is different from the Losartan Intervention for Endpoint Reduction (LIFE) study where a β-blocker was compared in a head-to-head fashion with an ARB. It is also different from the ASCOT study where a β-blocker/thiazide regime was compared in a head-to-head fashion with an amlodipine/ACEI regime, that is, the vast majority of treated hypertensives nowadays will already be on an ACEI/ARB (or be intolerant of them).

Others might consider that instead of adding a β-blocker, adding a statin to high BNP hypertensives might be more efficacious. However, there are 2 problems with that. First, statins only reduce cardiovascular events in some of the 4 of the cardiovascular abnormalities, whereas β-blockers may be effective in all 4 (see below), that is, statins are ineffective in LVSD (CORONA [Controlled Rosuvastatin in Multinational Trial in Heart Failure]) and GISSI-HF [Gruppo Italiano per la Sperimentazione della Streptochinasi nell’Infarto Miocardico–Heart Failure] trials), and in LVH. Furthermore, ischemia, where they are most valuable is only present in 17% of high BNP hypertensives. Second, huge numbers of optimally treated hypertensives needing primary prevention only are already on statin therapy, whereas few are already on β-blockers, for example, >70% were on antilipid therapy in the ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension) trial in 2008 and recent NICE (National Institute for Clinical Excellence) guidelines on statin use is likely to increase this markedly. A second possible intervention in high BNP/high-risk hypertensives instead of β-blockers might be aspirin but again, it would only be valuable in 1 of the 4 abnormalities (ischemia) and aspirin also has the downside of gastrointestinal intolerance and major bleeds. A third alternative intervention in high BNP hypertensives might be aldosterone blockade but it would only be effective in 2 of the cardiac abnormalities (LVSD and LVH) and, therefore, the risk of hyperkalaemia or renal dysfunction would pertain to many patients who might be receiving no benefit especially as they are likely to mostly be on concurrent ACEI/ARB therapy. In fact, there were increased adverse effects in ACCORD because of hyperkalaemia (9×) and renal failure (5×), which were presumably related to the use of aldosterone blockade on top of an ACEI.

**Treatment of Residual Risk: Ischemia and LVSD**

What evidence is there to suggest that adding a β-blocker would be beneficial if a patient harbored either silent ischemia, LVSD, LVH, or LAE? (Table). In the case of silent ischemia, Erne et al. showed that a medical anti-ischemic regime comprising mainly β-blockers (>80% of cases) but also other drugs reduced future cardiovascular events in silent ischemia by as much as 81%, with significant reductions in cardiac death, myocardial infarction, and angina in silent ischemia. Furthermore, a whole host of clinical trials in the 1980s showed the benefit of β-blockers when started after a myocardial infarction (MI). Observational data partially support the use of β-blockers in ischemia because in patients with stable ischemia, β-blocker use was associated with a 57% lowering of cardiovascular mortality in 1 study, although this has not been seen in another observational study. In the main meta-analysis of RCTs in stable angina, β-blockers reduced their 2 primary end points of total mortality (by 8%) and MIs (by 16%), although neither reached formal significance, which
might be because 75% of the patients compared with placebo in this meta-analysis were on oxprenolol, an old drug unique in having harmful intrinsic sympathomimetic activity (and incidentally the only β-blocker to worsen mortality in post-MI patients because of its intrinsic sympathomimetic activity). Thus, the use of β-blockers in silent ischemia overall looks promising, although it is far from certain.

As to LVSD, β-blockers are known to reduce cardiovascular events and deaths by 30% when LVSD is overt. The clearest indication that β-blockers should be beneficial also in asymptomatic LVSD comes from the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial where carvedilol reduced mortality in post-MI patients with (asymptomatic) LVSD. Furthermore, the general lesson of all past heart failure research is that neuroendocrine treatments, which are first shown to work in similar figures for calcium antagonists and diuretics, although β-blockers with (CAPERNICUS [Carvedilol Prospective Randomized Cumulative Survival]) to CAPRICORN).

Treatment of Residual Risk: LVH
As to LVH, β-blockers will further reduce BP to some extent, even when given to a patient at target BP and it is known that LVH is regressed when a lowered BP is achieved even in a patient with normotensive LVH. In meta-analysis, the absolute reductions in LV mass were 22.8 gm with β-blockers with similar figures for calcium antagonists and diuretics, although ACEIs were twice as potent. Further regression of LVH in such normotensive patients is likely to reduce future cardiovascular events. This assertion comes from subanalysis of the LIFE study by Okin et al and Wachtell et al, who also show that LVH is an independent culprit and that LVH regression per se reduces cardiovascular events. The reason extra BP reduction was ineffective generally in ACCORD might have been because any effect in patients with persistent LVH (despite target BP) was diluted out by the majority of patients in ACCORD not having LVH (or perhaps even not having any cardiac abnormality). ACCORD may have disappointed because of the lack of targeting of extra BP reduction to high-risk/high BNP patients. However, the stroke reduction (40%) in ACCORD was striking, meaning that the lower BP target of ACCORD almost certainly does deliver major benefits against strokes (see below) and there is a strong link between LVH regression and stroke reduction.

Treatment of Residual Risk: LAE
As to LAE, its main risk is that it produces new AF. In fact, a high BNP is associated with both new AF and a 6.7x increase in cardio embolic strokes. This new AF is likely to often produce a rapid ventricular rate, which can lead to acute, life-threatening heart failure requiring hospitalization. If such a patient with LAE and, therefore, at a high risk of developing fast AF, was already on a β-blocker, then even if AF did still develop, the ventricular rate is likely to be controlled from the start, which should avoid a life-threatening heart failure hospitalization because of fast AF. Another major advantage to their being on a β-blocker is that progression of AF from paroxysmal AF to sustained AF is reduced by slower heart rates. However, a potential downside is that the existence of their AF might not be identified for warfarin prophylaxis. However current evidence suggests that when anticoagulation is given to patients with silent AF, the fewer strokes are equally matched by major bleeds. This might be because silent AF is less of a risk factor for strokes than symptomatic AF, which means that anticoagulation may produce a lower absolute stroke reduction in silent AF while retaining the same hemorrhagic risk as in symptomatic AF. As a result, it is uncertain whether anticoagulants are of benefit in patients with silent AF and there are ongoing trials (the STROKESTOP study) addressing that question, which will report in 2019. Irrespective of the STROKESTOP study, the pulse should always be taken before prescribing a β-blocker and this necessary step should identify the worst cases of silent AF and eventually enable anticoagulation to also be started, if indeed the STROKESTOP study turns out to be positive. In other words, an indirect benefit of giving a β-blocker to high BNP/high-risk hypertensives is that it should lead to more of the worst cases of silent AF being detected simply because checking the pulse should be a standard step before prescribing any β-blocker to reduce the chance of tipping a bradycardic patient into needing a pacemaker.

A separate benefit for β-blockers here is that the antiarrhythmic effect of β-blockers might reduce the tendency for AF to develop in patients with LVH or LAE. β-Blockers might also be antiarrhythmic for other important arrhythmias. For example, LVH is well known to be an arrhythmogenic
substrate (and to increase sudden death 3-fold in Framingham). Therefore, the antiarrhythmic effect of β-blockers might reduce the tendency for ventricular tachycardia/ventricular fibrillation to develop in patients with LVH and thereby, reduce sudden deaths in patients with LVH, although this theoretical possibility needs to be specifically studied to see if it is true.

**Treatment of Residual Risk: Strokes**

A last possible benefit would be for the β-blocker–induced fall in BP to reduce future strokes. Because strokes are 75% higher in treated hypertensives than in equivalent normotensives, such an effect would be desirable and is possible for 2 reasons.1 First, in all epidemiology studies, BP is closely linked to the incidence of strokes (more than BP is linked to any other cardiovascular event). This is true all the way down to low systolic BPs of 100 to 110 mm Hg. Second and more convincingly, in the ACCORD trial, strokes were the only cardiovascular end point to be reduced by a lower BP target and the magnitude of this reduction was profound and significant by itself (41% reduction). Importantly an almost identical stroke reduction (44%) was the most prominent finding also in the UK Prospective Diabetes Study (UKPDS) when a lower target BP was achieved.46 It is crucial to note that the profound stroke reduction in ACCORD was seen within the normotensive BP range where a lower than normal target BP delivered this key benefit. It is in fact because of this major stroke reduction that some physicians think of the ACCORD strategy of a lower than target BP as being successful, although this is not the traditional view because stroke reduction was not the primary end point of the study. In a sense, the strategy of a lower target BP was highly successful at stroke reduction in ACCORD even when it was not particularly targeted to stroke-prone subjects. In this proposal, the ACCORD/lower BP strategy will be targeted to a high BNP group who are known to be stroke prone. We know that high BNP individuals are stroke prone because in a meta-analysis of 40 prospective studies, BNP independently predicted strokes with a hazard ratio of 1.93 (confidence interval, 1.58–2.37).12 The mechanism for this BNP/stroke link is probably multifactorial. First, they might have LAE that produces AF and cardio-embolic strokes. Second, the high BNP might be because of vascular disease elsewhere (eg, coronaries), which makes them prone to vascular disease in other sites. Third, the high BNP might be because of LVH, which is such a strong independent risk factor for stroke that echo LVH regression per se reduces strokes more (19%) than it reduced MIs (10%).28 In summary, the ACCORD/lower BP strategy was highly successful at reducing strokes even when it was not targeted to particularly stroke-prone individuals in ACCORD and, therefore, it will hopefully be even more effective here when it will be targeted to stroke-prone individuals. However, the achieved change in BP in ACCORD was −14 mm Hg and in UKPDS was −10 mm Hg, whereas β-blockers are likely to reduce BP by less than either figure. It would be hoped that better targeting (to stroke prone individuals) might offset the fact that the reduction in BP is less, so that the ultimate stroke reduction here might be close to that seen in ACCORD and in UKPDS (ie, a 40% reduction). In any case, the −14 mm Hg BP fall in ACCORD increased the incidence of serious hypotenion (17×) so that a lesser drop in BP might make the treatment more tolerable. Even if the level of stroke reduction is much <40% seen in ACCORD, it would still be worthwhile because strokes are, arguably, the main cardiovascular event to prevent because a disabling, severe stroke can be a fate worse than death and an expensive one for the health service at that. There is 1 possible caveat: in head-to-head studies comparing different antihypertensives in younger patients, calcium antagonists reduce strokes more than β-blockers. However, as described before, head-to-head studies are only tangentially relevant here because calcium antagonists are likely to be part of the baseline treatment of most hypertensives at target BP. Nevertheless, it is possible that increasing age might reduce the effect of β-blockers on stroke reduction.

**β-Blockers for Residual Risk**

Thus, there are a whole range of adverse cardiovascular effects (deaths, cardiovascular events, MIs, angina, heart failure, cardiovascular hospitalizations, and strokes) that might all be reduced with the addition of β-blockers in patients with either silent ischemia, LVSD, LVH, or LAE (Table). In effect, there are 5 different ways/mechanisms whereby β-blockers might reduce cardiovascular events in these patients (Table). Even if some of these 5 effects were weak, or nonexistent, the combination of 5 of them means that a reasonable reduction in cardiovascular events is a distinct possibility. In fact a combination of 5 weak effects might even deliver more benefit overall than 1 strong effect, which is what most drugs deliver.

A further issue is that, in the study by Nadir et al,13 two thirds of the 60% of patients with high BNP who had cardiac abnormalities had >1 (silent) cardiac abnormality and one third had >2 cardiac abnormalities. This makes it highly attractive to use a drug (a β-blocker) that simultaneously benefits several coexisting cardiac abnormalities. It is in fact rare in clinical medicine for 1 drug to be able to treat several different and coexisting abnormalities, but the use of β-blockers to treat all of ischemia, LVH, LVSD, and LAE is particularly attractive because it stands a good chance of achieving that unique distinction.11 Thus, in using a β-blocker in high BNP hypertensives, we would be using 1 drug to treat 5 different abnormalities, which frequently coexist in the target at risk population.

Of course, an alternative would be to phenotype each individual patient to identify which exact cardiac abnormalities are seen in each high BNP hypertensives and then treat even more selectively as according to the precise cardiac abnormality detected in each individual patient. Such an approach might superficially seem attractive, especially because there is a cohort of high BNP hypertensives (40%), who seem to have no cardiac abnormality at baseline. However, there are 3 reasons against it. First, it is likely to become cost ineffective if all high BNP hypertensives need to be phenotyped with detailed cardiac investigations. Second, phenotyping may not be that crucial because β-blockers are probably effective to some extent in all the important cardiac abnormalities (see above). Third, recent research reveals that those high BNP–treated hypertensives who have no apparent cardiac abnormality at baseline are about to develop LVH during the next few
The β-blockers are a pharmacologically diverse class of drugs. The use of atenolol and drugs with intrinsic sympathomimetic activity are associated with negative findings in the literature and, therefore, they may be best avoiding. However, this still leaves open many different β-blockers and no clear guidance can be given. One point of view could be that bisoprolol, carvedilol, or nebivolol seem equally effective in LVSD trials. The fact that these 3 drugs are all pharmacologically diverse in terms of β receptor specificity, α-blocking activity and vasodilatory NO activity could be seen as suggesting that ancillary properties over and above β blockade itself matter little.

Conclusions

Finally, β-blockers are exceedingly cheap drugs, which makes it particularly attractive to use them here, in the hope that they will reduce the impact of multiple (and often coexisting) cardiac abnormalities within a large section of the population (treated hypertensives). Overall, therefore this strategy could not only be effective but it could also be cost effective. Even if it turns out that β-blockers are only effective in half of these cardiac abnormalities and in only a quarter of the patients harboring them, the absolute numbers of cardiovascular events avoided could still be high and at an acceptable (low) cost.

Another way to look at this hypothesis is to say that it is now time to move BNP on from being a risk predictor to being a risk reducer. To do this, we ought now to explore interventions that look promising if given to high BNP/high-risk individuals. The most obvious intervention to explore first is β-blockers in high BNP hypertensives. This hypothesis now needs to be formally tested in a large clinical trial to see if the attractive theory above actually works in clinical practice and whether it outweighs its potential downsides. This will ascertain whether β-blockers when given to high BNP/high-risk hypertensives could be a major contributor toward achieving the 25×25 United Nations target (25% reduction by 2025) for reducing cardiovascular mortality.

Disclosures

None.

References

High B-Type Natriuretic Peptide Hypertensives at Target Blood Pressure: Potential Role of β-Blockers to Reduce Their Elevated Risk

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