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Arterial remodeling and hypertensive damage

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Valorization addendum

Introduction

The results presented in this thesis contribute to our knowledge about the etiology of high blood pressure (hypertension) and its associated cardiovascular outcome. In addition to their scientific value, these results also have potentially beneficial implications for society.

The cost of hypertension and cardiovascular disease

As already mentioned in Chapter 1 of this thesis, hypertension is one of the most important risk factors for cardiovascular diseases such as stroke, myocardial infarction, heart failure, and peripheral artery disease and is one of the leading causes of death. In addition, hypertension is a major cause of chronic kidney disease and dialysis and is involved in the development of vascular dementia. With prevalence rates of hypertension ranging between 22 – 46%, amounting to more than one billion affected people worldwide, hypertension is a significant public health problem. It has been estimated that 92 million disability-adjusted life-years (i.e. the number of life-years lost due to illness and disability) can be directly attributed to hypertension.[1] In the Netherlands, the costs of cardiovascular disease were € 11.6 billion in 2015, which corresponds to 12.3% of the total health-care related costs (RIVM, Statline Statistics) (Table 1). Although medication-treatment of hypertension accounted for 'only' € 694.3 million (0.6%) of total cardiovascular costs, 44% of cardiovascular costs were due to blood-pressure-related diseases such as coronary artery disease, stroke, and peripheral artery disease (Table 1). In a similar manner, kidney failure, for which hypertension is the second-most important risk factor, was also responsible for € 738 million (Table 1). Since it has been estimated that hypertension is directly attributable for 54% of

Table 1. Health care costs related to cardiovascular diseases in the Netherlands in 2015

Cost item	Costs (million)
Total health care	€ 94,424.2
Total cardiovascular diseases	€ 11,572.8
Hypertension (pharmacotherapy)	€ 694.3
Coronary heart disease	€ 2,406.1
Stroke	€ 1,636.2
Peripheral artery disease	€ 1,076.0
Kidney failure	€ 738.5

Source: Rijksinstituur voor Volksgezondheid en Milieu (RIVM) - Statline
https://statline.rivm.nl/#/RIVM/nl/dataset/50040NED/table?ts=1536508597364

the disease-burden of stroke and 47% of ischemic heart disease,[1] the total (indirect) costs of hypertension are therefore much higher. These numbers also show that the large majority of hypertension-associated costs are caused by its complications and late consequences. Since the prevalence of hypertension is rising worldwide, it is expected that, if left untreated, the socio-economic burden of cardiovascular diseases will rise to immense proportions. Therefore, developing efficient prevention and treatment strategies is a major priority in order to reduce ever expanding healthcare costs and morbidity.

Implications of understanding pathophysiological mechanisms

In order to develop novel preventive and therapeutic strategies, a thorough understanding of the mechanisms underlying the development of hypertension and its progression to hypertensive target-organ damage is required. Since arterial remodeling is thought to be a major pathophysiological factor in the development of both hypertension and hypertensive target-organ damage, the focus of this thesis was to investigate its role in different stages of essential hypertension. The findings in this thesis have not only confirmed this hypothesis (Chapters 3 and 4) but also show that changes in the vasculature such as increased renal and systemic arterial resistance occur relatively early in the hypertensive process (i.e. prehypertension) (Chapters 5 and 6). Although we have not presented research on novel treatment strategies in this thesis, these results have improved our understanding of the pathophysiology of essential hypertension. In the next paragraphs we will discuss the possible application and consequences of our findings in more detail.

Arterial remodeling as potential target for therapeutic intervention

In chapter 2 we reviewed several important mechanisms underlying arterial remodeling, learning from genetic diseases that are characterized by defects in specific regulatory proteins and which lead to a distinct vascular phenotype. These mechanisms could be a target for future interventions to reduce arterial remodeling and possibly also the development of hypertension and hypertensive target-organ damage. Since we found in this thesis that maladaptive arterial (carotid) remodeling is a relatively early phenomenon which is not easily reversible despite lowering of blood pressure (Chapter 3) and that aortic remodeling independently accelerates the decline in kidney function (Chapter 4), slowing down maladaptive arterial remodeling may have significant health benefits. One of the pathophysiological mechanisms, vascular calcification, is of particular interest in this regard. A key regulator of vascular calcification is the Vitamin-K-dependent Matrix Gla Protein (MGP) and absence or impaired functionality of MGP has been shown to induce extensive arterial calcification (Chapter 2). In line with these findings, our group has shown that inhibition of Vitamin-K by coumarin derivates

induces peripheral arterial calcification. [2] Based on these findings we are currently investigating whether supplementation of high-dose Vitamin K2 (menaquinone) reduces pre-existent arterial calcification. [3] If this hypothesis is confirmed, Vitamin K2 might become a novel pharmacotherapeutic option directly targeting arterial remodeling. As already mentioned in Chapter 2, in addition to vascular calcification, the other pathways may prove to be possible potential therapeutic targets, although further research is still required.

Prehypertension: to treat or not to treat

As already stated in Chapter 5, when studying the etiology of essential hypertension, one would ideally follow individuals before they develop hypertension. Since this is practically not feasible we focused in this thesis on participants who are in an early phase of the hypertensive process and can be labeled as being prehypertensive. We demonstrated in Chapter 6 that even in young prehypertensive volunteers, systemic and renal vascular resistance are elevated in comparison to normotensive controls, suggesting that arterial remodeling occurs even before high blood pressure has been established. Similar findings could be observed in Chapter 3 where active carotid artery remodeling was observed in still normotensive participants. Our results suggest that early intervention may prove to be beneficial in either slowing down maladaptive arterial remodeling or the development of complications. These findings are in agreement with other studies that showed that prehypertension is in itself a risk factor for developing overt hypertension as well as elevated cardiovascular risk (Chapter 5). [4] When considering that the majority of hypertension-related costs are generated by its late complications such as stroke or myocardial infarction, it is logical to assume that early pharmacotherapeutic intervention in the prehypertensive stage could be beneficial. In line with this, the 2017 ACC/AHA-guidelines lowered blood pressure thresholds for treatment-eligible Stage I hypertension to 130-139/80-89 mmHg if these patients have a concomitant cardiovascular disease or condition. [5] However, there are several implications of lowering the cut-off values defining high blood pressure. First of all it results in a significant rise in the prevalence of patients with hypertension and of the number of people that are now recommended to receive antihypertensive medication. For instance, in the US this would mean that 63% of people aged between 45 and 75 years would be labeled as being hypertensive, reflecting an increase of almost 27%.[6] From an economic perspective, the costs of hypertension are therefore also expected to rise significantly, but in the long term this may lead to lower costs resulting from fewer strokes or myocardial infarctions. A study evaluating the economic impact of implementing the 2017 ACC-AHA guidelines in Switzerland estimated an annual increase of € 60.3 million (22%) of the costs of antihypertensive treatment. [7] When extrapolating these numbers for the Netherlands, this would mean an increase of € 152 million per year for the treatment

of hypertension. In addition to elevated costs, labeling previously healthy people with a diagnosis is not without harm as Pickering pointed out, referring to a study by Haynes et al. in which labeling steelworkers with the diagnosis of hypertension was associated with a significant increase in absenteeism of work, as well as lower quality of marital and home life. [8] Such unintended psychosocial effects should be considered in implementing a screening or preventive program. Secondly, patients already being treated for hypertension would require more intense treatment in order to reach the lower treatment goals. Even with current cut-off values, management of hypertension remains a clinical challenge since only 50% of patients with established hypertension reach the desired blood-pressure goal. [9] Low adherence to pharmacotherapy and lifestyle intervention are major issues for many patients. It can be hypothesized that this problem may be even greater when a fairly asymptomatic disease requires intense treatment that is not without adverse side-effects. These considerations need to be evaluated before any public health campaign or screening program can be initiated. Nevertheless, our results and other evidence suggest that early treatment and prevention may give rise to a significant health benefit. Therefore cost-effectiveness has to be carefully studied before any recommendation can be made whether or not to screen and treat prehypertension.

Conclusion

In this thesis we investigated the role of arterial remodeling in the development of hypertensive target-organ damage in various stages of essential hypertension, including prehypertension. The results of this thesis have contributed to our understanding of the pathophysiology of essential hypertension and may have beneficial implications for future treatment and management strategies.

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