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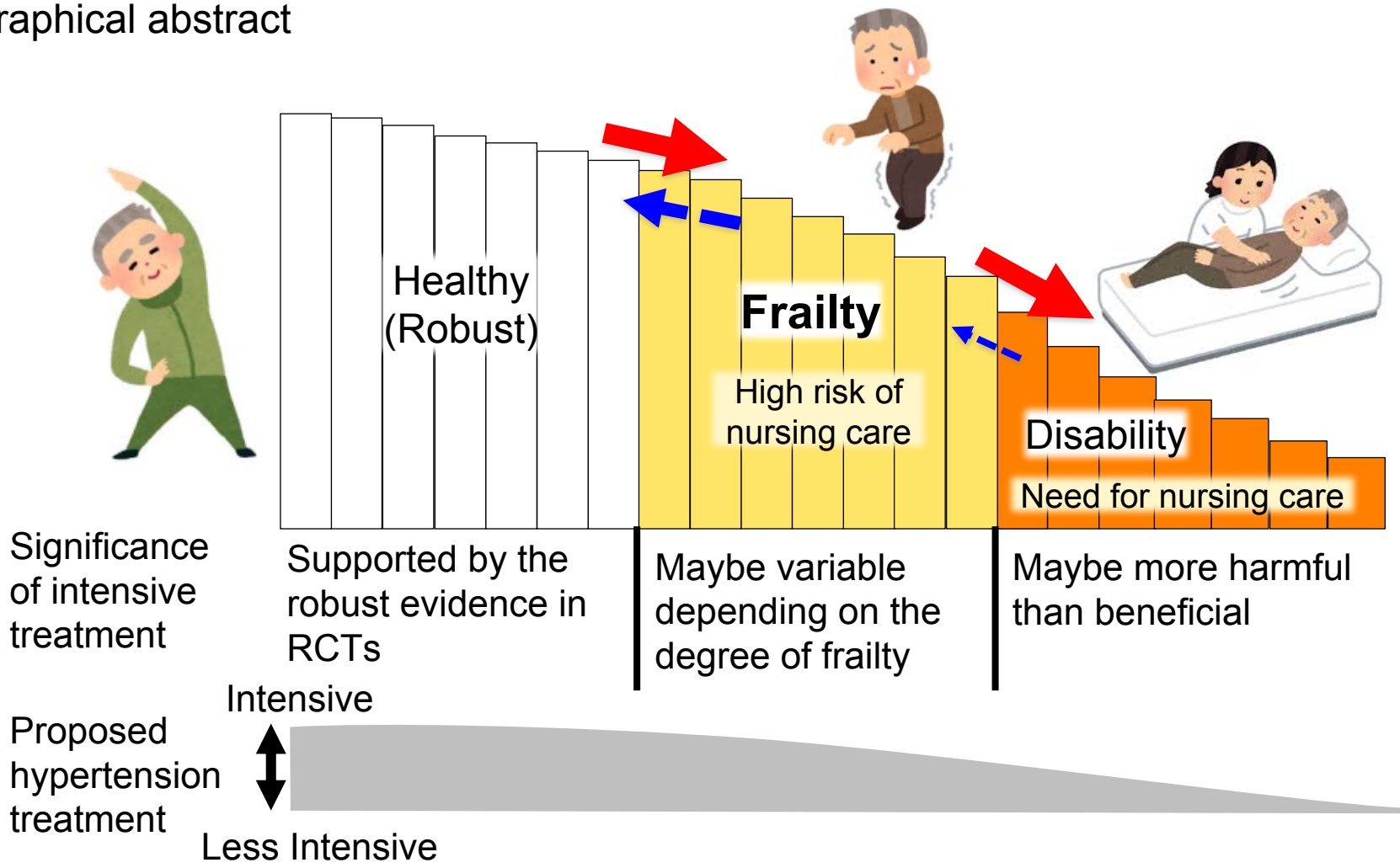
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Graphical abstract



Current issues in frailty and hypertension management

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For Review Only

Abstract

The significance of hypertension management in older individuals is greatly influenced by factors other than chronological age, as they have diverse physical, mental, and social backgrounds. Differences in physical functions, between independence, frailty and dependence, have a great impact on antihypertensive therapy in the older population. While recent clinical trials support the significance of intensive antihypertensive therapy regardless of age, there is little evidence to positively support the significance of antihypertensive therapy for older patients with physical function requiring nursing care, and observational studies suggest that antihypertensive treatment may instead be harmful in these older patients. Therefore, frailty, the transitional state between independence and dependence with the need for nursing care, is conceivable to be the tipping point at which the balance of risks and benefits of antihypertensive treatment is converted. The increased risk of acute adverse outcome is another issue that complicates management in the practice of hypertension treatment in frail patients. Particularly, increased blood pressure variability manifested by orthostatic hypotension in frail patients can induce fall and fracture leading to disability shortly after initiation or modification of antihypertensive treatment. Future challenges to optimize the management of frail hypertensive patients include developing techniques to estimate treatment efficacy, identifying safe antihypertensive regimens that reduce the risk of falls, and establishing strategies to restore frail patients to robust health.

Introduction

Frailty is a condition positioned between healthy robust status and disability requiring nursing care. In a geriatric medicine, frailty is important because it is a reversible condition that could be restored to a robust status with appropriate intervention, and frail patients are at high risk of adverse clinical outcomes including falls, fractures, hospitalization, worsened outcomes from chemotherapy or surgery, hemodialysis, disability and dependency, and mortality¹. There are two major classifications of frailty measures, phenotype models and accumulation deficit models including Cardiovascular Health Study (CHS) Index and Frailty index, respectively^{2,3}. Not surprisingly, aging increases both hypertension and frailty. The prevalence of hypertension is more than 60% in people over 60 years of age in Japan⁴. Also, the prevalence of frailty increases with age, particularly in people over 80 years of age, as pre-frailty and frailty increase and robustness decreases⁵. Given that both hypertension and frailty are potent determinants of human health and longevity, it is important to know how these conditions interact with each other in the management of hypertension.

This review introduces the importance of frailty in hypertension management by focusing on three topics. The first topic is how the significance of hypertension treatment varies depending on the physical condition of the older patients, including robustness, frailty, and disability. The second is what adverse events can occur when intensive hypertension treatment is given to frail patients. The third is why the significance of hypertension treatment varies according to physical function and what should be done in future.

Difference in the significance of intensive hypertension treatment by functional status in older patients

Recent guidelines for hypertensive management have recommended intensive treatment in robust older patients. In ACC/AHA hypertension treatment guideline in 2017, less than 130mmHg is recommended for noninstitutionalized ambulatory community dwelling older adults⁶. The 2018 ESC/ESH Guidelines for the management of arterial hypertension and the 2020 ISH global hypertension practice guidelines also set the treatment goal with less than 130mmHg if patients do not have frailty^{7,8}. In the recent Japanese guideline for hypertension (JSH2019), older patients who can consult an outpatient clinic by themselves in good health status are recommended to be treated with target BP recommended according to the age groups⁹.

These recommendations are undoubtedly affected by the SPRINT trial that showed clear clinical benefit of intensive treatment in patients including large scale of older patients¹⁰. This evidence was further supported by the recent STEP trial in China, which showed that intensive treatment is effective in older hypertensive patients in a setting similar to clinical practice, assessed by office blood pressure and involving patients with diabetes¹¹. The influence of frailty on the significance

of intensive hypertensive treatment has been the important issue to be discussed and subanalysis of older patients in SPRINT was done in this context¹². As a result, there was no heterogeneity in the benefit of intensive treatment by frailty determined by frailty index or gait speed, and the intensive treatment reduced the incidence of cardiovascular diseases similarly in patients with fit, less fit, and frail in patients over 75 years of age¹². The benefit of hypertensive treatment irrespective of frailty status is consistent with the subanalysis in hypertension in the very elderly trial (HYVET) in subjects over 80 years of age¹³. Therefore, it is suggested that, in randomized control trials (RCTs), intensive treatment is beneficial regardless of frailty status in older patients with hypertension. However, it should be noted that RCTs exclude older patients with disabilities and probably do not include patients with advanced frailty. Collectively, the significance of intensive antihypertensive treatment in older age is clearly supported by the evidence in RCTs if patients are robust or mildly frail, but these RCTs do not answer if patients with severer frailty or disability would benefit from hypertensive treatment (Fig. 1). Although there is no RCT to answer the question, observational studies might answer the question if these patients benefit from hypertension treatment. There are a lot of observational studies showing the association of BP and mortality in patients with frailty, and they obviously have shown that high BP is not associated with high mortality in patients with frailty. A meta-analysis of observational studies showed that the blood pressure less than 140 is associated with lower mortality in non-frail patients, but the association was not observed in frail patients with 1.02 of hazard ratio¹⁴. In 535 older hypertensive patients in a Japanese cohort study, mortality rates stratified by systolic BP and frailty status were the lowest in patients with systolic BP < 140 mmHg and non-frailty, followed by those with systolic BP \geq 140 mmHg and non-frailty¹⁵. In contrast, patients with frailty had the highest mortality regardless of the BP level, suggesting that frail patients have a poor prognosis regardless of their BP levels¹⁵. A recent study showed the association between systolic BP and mortality in older adults with or without frailty determined by frailty index¹⁶. It was clearly shown that in non-frail participants, the relationship between BP and mortality shapes the J-curve and mortality increase with both high and low BP. In contrast, in frail participants, this J curve relationship disappeared and high BP was unilaterally associated with lower mortality¹⁶. Nevertheless, there is an unignorable consideration in interpreting the results of observational studies because it is hard to know the causal relationship between BP and mortality. In this context, there is an observational study implying the causal relationship between the intensive treatment and increased mortality in patients with disability. In this study, the subjects in nursing home were classified into four groups based on having a systolic blood pressure of more or less than 130 mmHg and more or less than two antihypertensive medications¹⁷. As a result, the highest mortality was observed in subjects with low SBP with two or more antihypertensive medication was observed, suggesting that intensive antihypertensive treatment may be harmful in patients

requiring nursing care¹⁷. Although these results should be clarified in future studies, preferably based on RCT designs, it is conceivable that intensive medication in hypertensive patients with disability may be more harmful than beneficial. Thus, the balance of benefits and harms of antihypertensive treatment in frail patients may vary with the degree of frailty (Fig 1).

This concept is actually reflected in the guidelines, which recommend that patients with advanced frailty or disability need to be treated differently than those who are ambulatory and robust⁶⁻⁹. European geriatrician also proposed a decisional algorithm for the management of hypertensive patients over 80 years of age by considering the different treatment approach based on physical function¹⁸. We also proposed a flowchart-based management that recommends treatment of older hypertensive patients according to the presence or absence of functional dependence and the degree of ADL impairment in frailty¹⁹. Then, how can we evaluate frailty and ADL impairment in clinical practice? The frailty assessment mainly used in Japan is J-CHS criteria as shown in table 1^{19,20} and a decrease in walking speed can be estimated by answering "no" to the question "Can you cross over at the pedestrian crossing?"¹⁹. Instrumental ADL impairment can be screened with the question "Did you visit clinic without the need for an escort?" in outpatient clinic. If "no", the Instrumental Activities of Daily Living Scale (IADL) can be used for further assessment²¹. Basic ADL impairment can be screened with the questions "Do you need help for bathing?" and "Do you have urinary incontinence?". If both are "yes", the Barthel Index can be used for further assessment²².

An adverse consequence of intensive hypertension treatment in patients with frailty

Difficulties in hypertension treatment in patients with frailty include not only the question of benefit in long-term clinical outcomes, but also the risk of short-term adverse events, particularly fall and fracture. A 2-year prospective observational study with and without frailty in Ireland reported that hypertensive subjects with frailty defined by the CHS index increased risk of falls or fractures by intensive treatments after adjustment for age and gender, but not after addition of all confounding factors²³. In the analysis of 5236 participants ≥ 65 years taking antihypertensive medication in a population-based cohort in the United States, the risk of serious fall injury increased with the number of frailty indicators after multivariate adjustment²⁴. In this study, systolic BP, diastolic BP, and number of antihypertensive medication classes being taken at baseline were not associated with risk for serious fall injuries²⁴. The risk of falls and fractures may be greatest early after initiating or increasing antihypertensive medications, as suggested by the study that the risk of fracture increased for 45 days after the first prescription for antihypertensive medications but not for 45-90 days in community dwelling older hypertensive patients in Canada²⁵. These findings call attention to the fact that antihypertensive therapy for frail patients is a double-edged sword that can induce fractures, a direct cause of disability.

Why is the significance of hypertension treatment altered by physical function?

The reason why the significance of hypertension treatment is altered by frailty is not fully understood, but the potential influence of frailty on BP regulation is explained by that physical frailty is associated with increased arterial stiffness and reduced body fluid volume due to muscle loss^{26,27}. These factors could increase BP variability and induce a gradual downward trend in mean BP. In fact, the frailty has been shown to be associated with BP variability as shown by the increase of orthostatic hypotension (OH). The analysis of a head-up tilt table test on 496 patients admitted to a geriatric clinic showed that approximately 30% of patients experienced OH within 5 minutes, with the greatest difference in robust, pre-frail, and frail status as defined by a CHS index after 1 minute²⁸. In the CHS index, slowness with low walking speed and weakness with low grip strength are associated with increased OH within 1min²⁸. It was also shown that in 168 geriatric outpatients (mean age 81.4±7.0; 55.4% female) in Netherland, CHS-frailty and number of falls are both independently associated with high systolic BP drop rate in 0-15 seconds, but not in 15-180 seconds²⁹. Of note, recent studies showed the specific BP trajectory in the long period before death in older age³⁰⁻³². A study using electronic medical records of 46634 individuals who died in the United Kingdom between 2010 and 2014 at age 60 or older showed a trend toward lower blood pressure around 10 years before death, and this trend was augmented by increased baseline frailty³².

Figure 2 illustrates the overall schema to explain the relationship between BP and treatment benefit of hypertension in the life course of older age. Together with the increased trend of BP in early stage of aging, BP follows an inverted U shape trajectory from older age until death and this trajectory should be accompanied by the development of frailty. **As frailty progresses, BP fluctuations that could cause orthostatic hypotension will also increase, leading to the increased risk of falls or fractures. Thus, the balance of benefits and harms of hypertension treatment is expected to change dramatically over this life course.** Accordingly, the goal of hypertension treatment will shift from improved prognosis to suppression of extreme BP elevations and even lack of need for treatment. Therefore, the magnitude of hypertension treatment needs to be modified based on the significance of hypertension treatment at each life stage.

Future perspectives

Based on the above discussion, there are several issues that need to be resolved in the management of hypertension in frail patients. First, the benefit-harm balance of intensive antihypertensive treatment is expected to reverse as frailty progresses, but no markers have been established to date to predict the tipping point between harm and benefit. Further investigation, including digital biomarkers that quantify changes in blood pressure in response to physical

activity, may be required to estimate the balance of benefit and harm of treatment in frail hypertensive patients. **Second, the potential harms of antihypertensive treatment on people with advanced frailty or disability have yet to be determined in RCTs. In this context, the ongoing RCT "RTREAT-FRAIL" will examine the impact of antihypertensive drug reduction on all-cause mortality as a primary endpoint in nursing home residents aged 80 years or older, with SBP less than 130 mmHg and prescribed at least one antihypertensive drug³³. This study was designed based on the above-mentioned observational studies suggesting the harmful effects of intensive hypertension treatment in older people who require nursing care¹⁷.** **Third,** evidence is insufficient to provide recommendation on how to safely treat hypertension to prevent acute adverse outcomes, including falls and fractures. Evaluation of orthostatic hypotension and starting medications at low doses are available strategies, but information on the classes of antihypertensive medications that minimize the risk of adverse events needs to be established by future evidence. Finally, given that frailty is a reversible condition that could be restored to a robust status, the development of strategy for the treatment of frailty is desired. To date, the combination of exercise and nutrition is the only evidence-based strategy of frailty treatment³⁴. Further research is needed to develop new strategies for treating frailty, including pharmacotherapy.

Conclusion

While recent RCTs on hypertension treatment have highlighted the importance of intensive treatment regardless of age, it is increasingly important to understand that the significance of antihypertensive treatment changes dramatically as functional decline progresses in old age. In this context, frailty deserves special attention because it is a physical condition that can be the tipping point between the benefits and harms of antihypertensive therapy. Antihypertensive therapy for frail patients should be initiated or modified with extreme caution because of the potential risks of falls, fractures, and subsequent transition to disability. Clinical manifestations of BP variability in frail patients involve orthostatic hypotension, and BP measurement immediately after standing can be useful to estimate the risk of falls. Finally, further studies will be needed to optimize the management of frail hypertensive patients, including developing technologies to estimate treatment efficacy, identifying safe antihypertensive regimens to reduce the risk of falls, and, most importantly, establishing strategies to restore frail patients to robust health.

Conflict of Interest

The author has no conflict of interest to declare.

Table 1. J-CHS criteria

Items	Definition
Shrinking	Unintentional weight loss ≥ 2 kg/6 months
Weakness	Grip strength: men < 28 kg, women < 18 kg
Exhaustion	Constant tiredness in the past 2 weeks
Slowness	Usual gait speed < 1.0 m/s
Low activity	1) Low levels of physical exercise < 1 day/week 2) Regular physical activities < 1 day/week Applicable to both questions
Assessment: Robust: 0, pre-frailty: 1–2, Frailty: ≥ 3	

Figure legend

Fig 1. Transition in functional status in old age and the significance of intensive antihypertensive treatment

Fig 2. BP trajectory, functional status, and temporal changes in the significance of hypertension treatment in old age

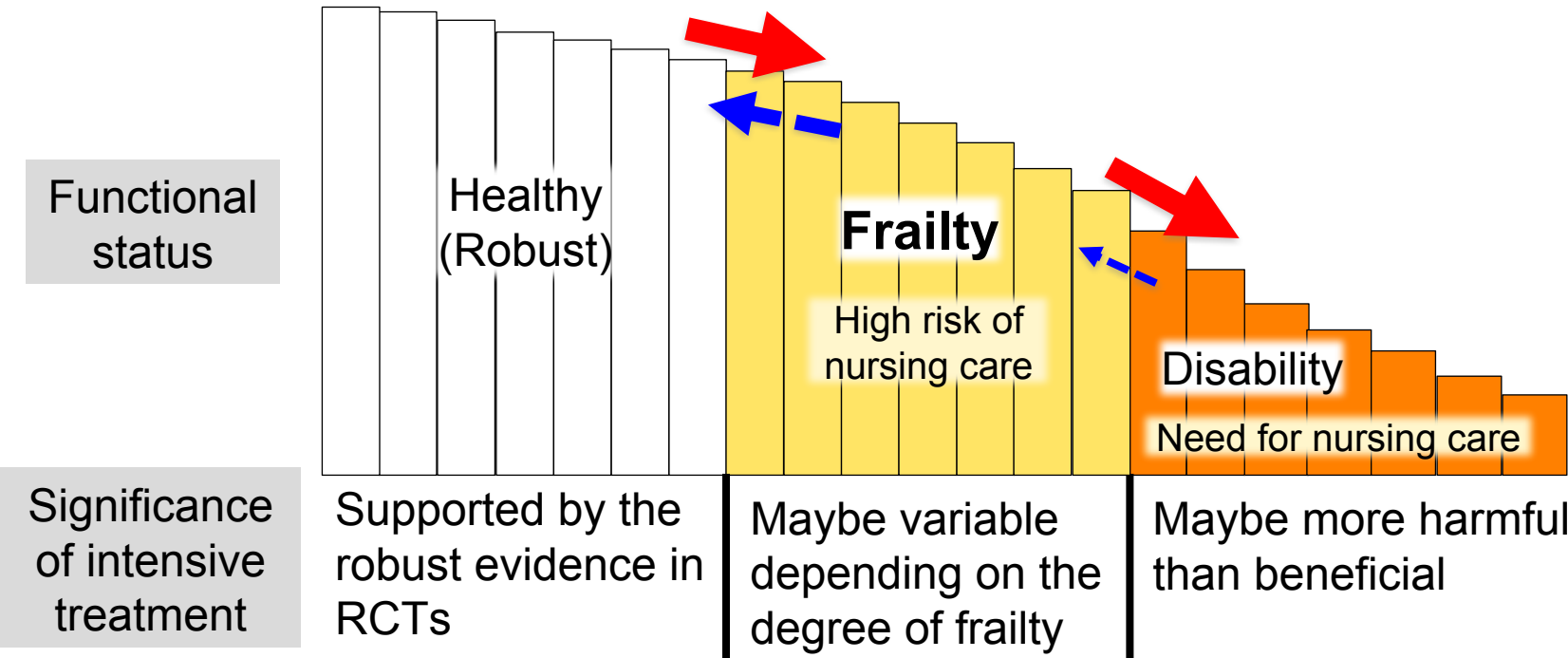
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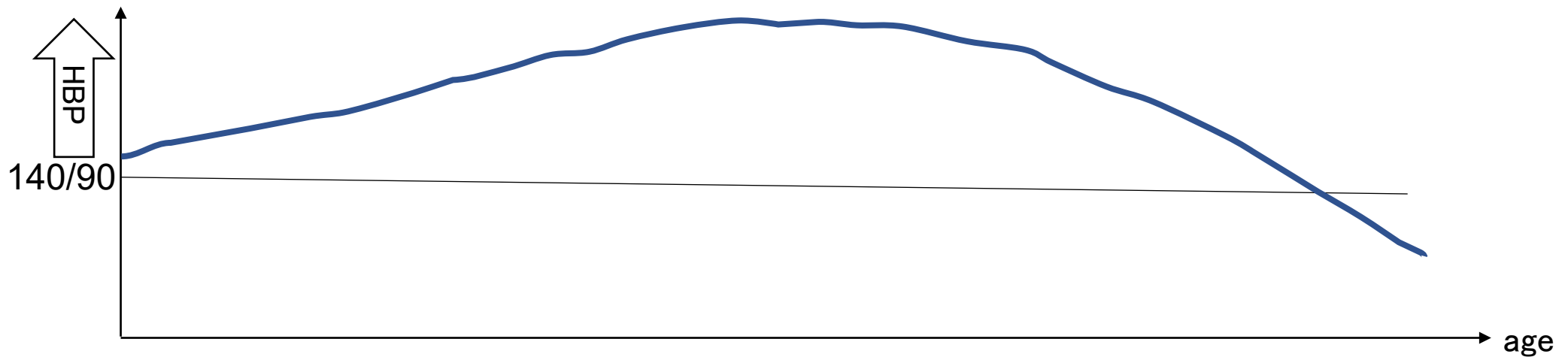
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Figure 1.



BP



Robust

Frailty

Disability

BP variability

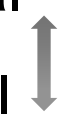


Orthostatic hypotension



beneficial

harmful



hypertensive treatment



Improving prognosis

Preventing extreme BP elevation

No need of treatment

Intensive

Less Intensive



Proposed magnitude of hypertension treatment

