Atherosclerosis: The 21st Century Epidemic
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Hypertension: Why is it Poorly Detected and Poorly Treated?

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Is hypertension a significant vascular risk factor?

Hypertension is a highly prevalent disease. There are more than one billion hypertensive people worldwide [1]. The lifetime risk of developing hypertension is 90% at age 50. The age adjusted mortality from hypertension has increased 53% over the last decade and high blood pressure accounts for 54% of strokes and almost 50% of coronary cardiac events [1]. This compares to cholesterol accounting for approximately 15% of strokes and a similar proportion for smoking. Hypertension is especially concerning in women because one out of two become hypertensive at age 55, yet, most are unaware of this fact and concerned about hypotension which is a common problem among young women. This diagnosis delay results in missing valuable years of treatment. Recent studies from Canada show that only 16% of treated patients were controlled [2]. Different studies from other world regions including low and high-income countries show the same proportion of poorly controlled patients under treatment. Hypertension results in a six fold increase in stroke risk, which is only comparable to that caused by atrial fibrillation, and is only lower to have suffered a previous stroke. Hypertension results in 7 million deaths annually, which imply 13% of all deaths worldwide [3-7]. Importantly the Framingham study has shown that treatment of moderately increased high blood pressure significantly reduces the risk of cardiovascular events. This is consistent with the notion that most vascular events occur in people with few risk factors.

The preceding data strongly supports the notion that hypertension is the most important modifiable risk factor. However, only 2 out of 3 patients are diagnosed and 1 out of 3 patients diagnosed and treated are controlled. Only 25 to 50% of hypertensive patients receive treatment in North America and Europe, 50% of patients admit not taking medications properly, and 50% of patients adjust the medication based on self-measured blood pressure [8-10].

An important issue that contributes to poor compliance is the 'poison pill' effect in which the patient will not only tend to stop a medication causing side effects but also medications prescribed for other pathologies [11]. Although different studies have shown similar effectiveness for all antihypertensive drug classes, there is a different side effect profile for each of

these drug groups. Therefore, the appropriate drug selection to minimize the incidence of side effects is crucial. As an example, diuretics cause more frequent side effects than angiotensin receptor blockers (ARB). Thus, if a diuretic is the only hypertension treatment, side effects could result in the so-called 'poison pill' effect.

A different approach to show the effectiveness of hypertension treatment is the NNT (number needed to treat) (Figure 1, see p. 182). In the case of secondary prevention where a larger therapeutic effect is expected, in symptomatic carotid stenosis 8 patients have to be operated over 2 years to prevent 1 stroke. With aspirin, 55 patients have to be treated for 2 years to prevent an MI or 200 patients will have to receive aspirin for 2 years to prevent 1 stroke. In primary prevention, the numbers have lower power and in asymptomatic carotid stenosis, 83 patients have to be operated over 2 years to prevent 1 stroke. Numbers are more conspicuous for scenarios such as atrial fibrillation where 66 patients have to be treated with anticoagulants for 1 year to prevent 1 death. Focusing on hypertension, 30 patients (average BP 140/90 mmHg) have to be treated for 5 years to prevent 1 death and for people older than 80 years, only 40 patients have to be treated for 2 years to prevent 1 death. The aforementioned numbers clearly reflect the significant benefit of treating even slightly hypertensive patients.

What is normal blood pressure?

The VII Joint Commission (2003) has defined 130/80 mmHg as 'normal' blood pressure [1]. However, this value as a definition of normal has changed in the past and is likely to change in the future. Moreover, the lower threshold at which the relationship between cardiovascular mortality and blood pressure no longer applies has not been identified. The concept of 'pre-hypertension' adds confusion in the non-expert medical and general population. Many interpret this concept as encompassing the still-not-hypertensive but data shows that 16% of hypertension-related deaths occur in 'pre-hypertensives' [12]. In fact, blood pressure is a continuous risk variable and as such the relative risk for cardiovascular events progresses with increasing values starting at a systolic pressure close to 110 mmHg [13,14]. The lowest blood pressure value at which cardiovascular risk disappears has yet to be defined. Data from various studies have suggested that in diabetes mellitus the blood pressure threshold considered normal is probably lower than the value for the general population. The ACCORD study recently analyzed a subgroup of approximately 5000 patients randomized to an intensive blood pressure treatment group with a target systolic value of less than 120 mmHg versus a standard treatment group (BP less than 140

mmHg) [15]. The BP differential achieved was 14 mmHg. However, the study failed to show a significant difference favoring the primary endpoint of stroke MI, and death. A caveat is that the control group had a 50% lower rate of events than expected. This widened the confidence intervals and thus the statistical power of the study significantly dropped below the initially calculated value. This methodological shortcoming questions the validity of the study results. Interestingly, stroke was reduced (although not statistically significantly) in the intensive treatment group. Moreover, a limited treatment time and the fact that both groups had BPs close to 'normal' may have contributed to the negative study results.

In 2009, Law *et al.* published a meta-analysis of anti-hypertension treatment that evaluated 464,000 patients in 147 studies [16]. One of the important observations in the analysis was that 119 of the studies included patients with pre-treatment values lower than 140/90 mmHg. Despite this large number of patients with normal BP, the authors reported a 50% cardiovascular risk reduction for each 5 mmHg reduction in diastolic blood pressure. Based on this benefit, they concluded that BP reduction should not be limited to people with high blood pressure. Most important, the percentage reduction in coronary heart disease and stroke was similar regardless of blood pressure before treatment and down to a BP of 110/70 mmHg.

Another meta-analysis including 1 million patients from 61 cohorts and no previous cardiovascular disease showed that death rates doubled for each 20/10mmHg systolic and diastolic pressure increments [17]. The risk of cardiovascular death associated with BP was observed down to a pressure of 115/75 mmHg. A valuable observation from both meta-analyses is that it is not that risk was not observed below the 110/70 value, but rather that there were not enough patients in that group to make any conclusions. Nor was there suggestion of a 'J' shaped curve revealing increased risk below the lowest blood pressure associated with cardiovascular morbidity. In a study by Verdecchia, 1000 patients were randomized to a group with BP below 130 mmHg systolic or to another with BP below 140 mmHg [18]. The primary endpoint of left ventricular hypertrophy was significantly lower in the tight control group and secondary endpoints (all cause mortality, fatal or non fatal MI, fatal or non fatal stroke, TIA, CHF, AF, CABG) also favored tightly controlled BP. Another finding that is important to underscore is that there were no significant differences in side effects between groups. The NIH has planned the SPRINT study on 7500 patients older than 55 years with no stroke (SPS 3 is including these patients) or diabetes (included in ACCORD) [19]. One group will be randomized to a systolic of 120 mmHg or less with an average of 4 anti-hypertensive drugs versus another

group with BP under 140 mmHg using an average of 2 drugs. The study is expected to last 9 years and will cost approximately US$ 100 million. Assessment of cognitive function will be included in the analysis.

In summary, the above data supports the axiom that the lower the blood pressure the better. However, we should be concerned to define how many vascular events are occurring in people that have their BP between that to be defined as 'ideal' in ongoing and future studies and the current 130/80 mmHg presently considered normal.

Are hypertension effects proven and understood?

The etiology of hypertension is related to multiple genes and environmental factors. Despite this, the available treatment is highly effective. A wealth of studies over the last 20 years has shown a major decrease in stroke and MI in treated patients [20-27]. A decision to terminate some of the studies was due to the large beneficial effect in the treatment versus the placebo groups. HYVET was a landmark study done on almost 4000 patients older than 80 years of age with a sustained systolic BP of 160 or more [28]. Patients were randomized to the diuretic indapamide with or without perindopril versus placebo to achieve a BP of 150/80 mmHg. Although without the support of scientific evidence, the usual recommendation has been to limit hypertension treatment in this age group to avoid medication side effects and other complications attributed to lowering BP (cognitive dysfunction, precipitating stroke or MI). The primary endpoint of HYVET was positive for a significant reduction in cardiovascular death, stroke, and CHF. There was also an unexpected reduction in death from any cause. Unexpectedly, and challenging current dogma, fewer side effects occurred in treated patients.

The previously mentioned meta-analysis by Law also adds to the knowledge on hypertension treatment effects. In this meta-analysis there were 22,000 coronary events and 12,000 strokes [16]. There was a 22% reduction in coronary heart disease and a 41% stroke reduction with each 10/5 mmHg decrease in systolic and diastolic BP respectively. The analysis also showed that all 5 drug classes had similar effects. There was an additional 25% reduction in CHF. Patients receiving 3 drugs at 50% the standard dose had a 46% decrease in coronary heart disease and a 62% reduction in stroke compared to one drug given at the usual standard dose, which had 50% of the aforementioned effects. This means that it would be preferable to use multiple drugs at a lower than maximum dosage since this is likely to cause a greater therapeutic effect with a lower incidence of side effects and therefore of drug discontinuation. The meta-analysis also showed that the percentage reduction in coronary heart disease and stroke was similar in

patients with and without history of cardiovascular disease. This has the important implication that there was an equal effect for primary and secondary vascular prevention. Comparing the results of this meta-analysis and that of individual trials in BP lowering it becomes clear, observing the causal relation between blood pressure reduction and benefit, that the effect of these medications in reducing vascular risk is almost entirely due to their BP lowering properties. This is in contrast to statins and other medications that, in addition to their expected effect, have indirect pleiotropic action. Data accumulated in recent years suggests a significant interaction between hypertension and cognitive dysfunction beyond that associated to the presence of cerebral infarcts and dubbed 'vascular dementia'. Dai *et al.* from the University of Pittsburgh studied 40 patients with normal cognitive status who had their cerebral blood flow measured with CASL-MRI (continued arterial spin labeled MRI) [29]. Twenty had hypertension under treatment and 20 were normotensive. Results showed a statistically significantly decrease in cerebral blood flow in the hypertensive patients but no change in blood flow in the normotensive patients. Most interestingly, the decrease in blood flow was noted in areas related to Alzheimer's disease: limbic and paralimbic structures and other frontal and sub cortical cerebral regions. The authors concluded that hypertension could lead to a vulnerable brain state to develop degenerative dementia.

Despite all the information available on the significant reduction of cardiovascular events secondary to high blood pressure treatment, hypertension is usually not detected or is detected but not controlled.

Hypertension is not detected

Physicians, patients and equipments for BP evaluation encompass all the players in BP assessment that may lead to measurement errors. A statement by the American Heart Association published in 2005 evaluated in detail all BP measurement devices [30]. Sphygmomanometers with mercury are being abandoned or banned and the use of aneroid machines is associated with different operator-related measurement errors (visual, auditory, terminal digit preference) [31-33]. Electronic devices are probably the most reliable equipments. We have also found that it is helpful to show the patients the BP numbers in the screen to increase awareness of the implications of these values. These automated oscillometric devices allow an increase in the number of readings and decrease observer-related errors. Patients may also have responsibility in the inaccuracies of BP measurement. One German study entitled 'Manipulation of BP self-monitoring values' randomized 48 patients to a group that was aware that the electronic device given by the

investigators to the patients had a storing capacity and another group unaware of this machine's capability [34]. The investigators asked the patients to take their BP twice in the morning and in the evening and to make a written log of the measurements, which they analyzed after a few weeks. The agreement rate between stored and reported values was significantly lower in the 'unaware' group. The reasons were due both to the use of fictional data in which patients simply invented numbers without measuring their BP and to inadequate reports in which patients would measure their BP enough times until they obtained a normal result, which was the one they wrote down in the BP log.

However, the deadliest myth about BP measurements lies on the medical side and is the so-called 'white coat' or 'office' hypertension. Mancia in 1983 described this phenomenon in patients that showed increase BP values when measured in the office by a physician compared to the same patient's values measured at home [35]. Most physicians consider that these increased values at the office are 'harmless' and take no specific action or treatment to correct them. Different studies have shown that measurements at home and with a 24 hr Holter provide similar results and are both lower than office recordings [36]. The problem of this indifferent medical behavior with high office recordings is its conflict with a myriad of studies showing that isolated hypertension in the office is as harmful as sustained office- or home- hypertension. Different studies show similarly increased carotid artery intimal-media thickness (IMT) in isolated office hypertension and sustained hypertension; a study on 1200 patients with a 20-year follow up showed increased stroke risk in those with isolated systolic hypertension; arterial stiffness and left ventricular size increase similarly in patients with 'white coat' and sustained hypertension; microalbuminuria, retinopathy, IMT and LVH were seen in similar proportions in patients with 'white coat' and sustained hypertension; and 'white coat' hypertension occurring during mental stress and mathematics was a stronger predictor of atherosclerosis progression than smoking and cholesterol levels [37-43]. A recent meta-analysis on 11 studies confirmed the higher risk of coronary heart disease, stroke and death in patients with 'white coat' hypertension compared to the normotensive population [44]. The risk of developing sustained hypertension is significantly higher in patients with 'white coat' hypertension [45]. A recent study from Australia followed almost 9,000 patients in 11 centers with the aim of identifying which were the ambulatory BP equivalents to clinic BP thresholds for the diagnosis of hypertension [46]. The authors found that when patients had a BP of 150/100 mmHg at the clinic, they had 8/4 mmHg less in systolic and diastolic BP respectively during

ambulatory measurement. When clinic BP was 140/90 mmHg, the ambulatory BP was 4/3 mmHg less and when BP was 130/80 mmHg (i.e. normal) at the clinic, ambulatory BP was 2/2 mmHg less. These findings showed that there was no significant difference between ambulatory and clinic BP measurements and, importantly, that the closer to normal the BP, the greater the agreement in ambulatory and clinic BP. This implies that a patient who has a BP of 150/95 mmHg measured at the office should not be expected to have a large difference such as 120/70 mmHg at home or during ambulation as a reliable measurement. Thus, patients may have a higher BP at the clinic when measured by a physician (BP measured by a nurse compared to MD recordings was usually slightly lower) but these expected differences do not justify the large gaps consistently obtained when clinic BP is compared to that reported by patients. Interestingly, all the evidence showing that hypertension damages different organs is based in studies done using BP measurements made by medical staff at the office or clinics. In addition, most of the evidence proving that treatment of hypertension is beneficial is based on measurements done mostly at the office or at clinics by physicians. The practice to tell patients that high BP obtained at the clinic does not require treatment because it is a benign phenomenon reflecting a 'nervous' reaction to the measurement is a fallacy. The data available suggest that office or 'white coat' hypertension is hypertension.

On following the question about reliability of patient self-BP measurements, we performed a study in 200 patients in Argentina measuring BP at the clinic in 4 different visits over 6 months [47]. BP rates above 140/90 (used as limit for normal BP) were close to 80% in all visits despite adjustment of treatment. At first visit measurements, 60% of the patients had BP values above 160/100 mmHg. The study included another BP measurement self-reported by the patients, 1 week after visit 1 at the clinic and 3 weeks before visit 2. For this measurement, patients were asked to have their BP taken at home or any other place and call the office with the result obtained. Not surprisingly, only 38% of the self-reported values were above 140/90 mmHg, there were no measurements equal to or above 160/100 and 44% of the reported values were equal to or lower than 120/80 mmHg.

As a follow up of this report, we selected a large group of 20,000 patients randomized in the PROFESS study (C. Estol personal communication). In this analysis, BP at visit 1A (self-reported by the patient) was statistically significantly lower than BPs measured at visit 1, 2, 3 and 4 at the clinic (by physicians) similarly to what we found in the smaller Argentine study. There was a significantly higher report of falsely 'normal' BPs measured outside the clinic.

Hypertension is detected but not controlled

In 2005 we reported a study made at a Neurology Clinic on 670 patients with an average BP of 142/86 mmHg measured at visit 1 [48]. Of all patients evaluated, 59% were hypertensive at the 1st visit (23% had a BP higher than 160/95 and 12% had a BP greater than 180/105). Among those that did not have a previous diagnosis of hypertension, 54% were hypertensive and of the 37% of patients with a previous diagnosis of hypertension, 83% were hypertensive implying that BP was treated but not controlled. We referred most patients to their MDs for treatment of hypertension but at our neurology clinic follow up 95% had no change in their BP treatment. We designed a new study starting in 2005 but this time we treated hypertensive patients at the neurology clinic. Neurological diagnosis of the patients included: 16% stroke, 14% headache, 14% dementia, 13% movement disorders, 10% spine problems and other neurological diagnosis [49]. We found that of the 1,464 patients included in the study, 500 had a prior diagnosis of hypertension yet their average BP was 160/93 mmHg with only 76 patients (15%) under control. These results reproduce the same rates of hypertensive population that achieve normal BP values under treatment in other world regions. Among the 1,000 patients that did not have a prior diagnosis of hypertension, 577 (60%) had an average BP of 151/93 and only 382 were truly normotensive. In total, 70% of the patients were found hypertensive during the 1st visit at the neurology clinic. They all had their treatment adjusted by a vascular neurologist or a cardiologist. Of the 544 that returned for follow up, the BP decreased in average from 155/93 mmHg to 143/86 mmHg and in 222 the BP reached an average of 123/78 mmHg. The average decrease in BP was 12 mmHg systolic and 7 mmHg diastolic and the difference in BP achieved at the Neurology Clinic was significantly better compared to BP control outside the Neurology Clinic.

Conclusions

Several factors limit implementation of available knowledge on effective hypertension treatment. These barriers should be identified to define strategies that could overcome them. Difficulties to treat hypertension effectively similarly affect high and low income countries. Although better economies possibly contribute to improving BP management, they do not necessarily address the various social and cultural factors that play a role on poor BP control. A feasible initial approach is to favor the creation of 'Vascular Clinics' with the active participation of stroke, cardiology, diabetes, lipid and other vascular specialists over individual 'Stroke Clinics'. In addition, the population in general (physicians and patients) is not taking 'seriously' the

results of BP measurements. The adequate behavior should be to treat BP values every time they are found elevated and avoid a watchful-waiting attitude. Since two meta-analyses including 1.5 million patients have shown benefit with BP reduction even in normotensive patients, BP should be readily treated even when slight hypertension is diagnosed. BP measurements should be done at clinics by adequately trained medical personnel and, ideally, patients should not be asked to control their BP due to the significant issues that result in inaccurately reported values. An alternative is to change BP measuring systems since present methods, even electronic devices, use numerical scales that confuse the result interpretation by patients. A medical statement against the 'white coat hypertension' concept should be published explaining that high blood pressure measured at a clinic corresponds to a slightly lower pressure measured at home but when the BP is equal or above 140/90 mmHg at the clinic the evidence supports pharmacologic treatment. Current studies are addressing the issue of 'normal blood pressure' to define the lowest value that is not associated with an elevated cardiovascular risk. Most physicians can and should treat hypertension. The high prevalence worldwide of patients with abnormally elevated BP is unacceptable and reveals a concerning degree of neglect in which the medical community has most of the responsibility.

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NNT: AN EXAMPLE COMPARING HYPERTENSION AND OTHER TREATMENTS

		YEARS	EVENT	NNT
NASCET	>70%	2	Stroke	8
NASCET	50-69%	2	Stroke	20
NASCET	<50%	2	Stroke	67
ACAS	>60%	2	Stroke	83
Aspirin	Prim Pr.	5	MI	200
	Second	2	MI	55
		2	Stroke	200
		2	death	83
Statin	Second	2	Stroke	52
		2	MI	58
AF		1	death	66
		1	Stroke	33
Exercise		1	death	333
Hypertension	BP 140/90	5	death	30
HYVET	BP 150/80	2	death	40
	BP 180/110	5	death	19

Figure 1.