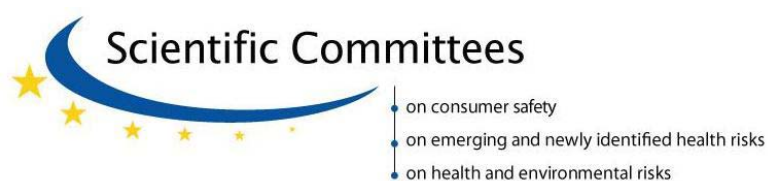




Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Mercury Sphygmomanometers in Healthcare and the Feasibility of Alternatives



SCENIHR adopted this opinion at its 4th plenary of 23 September 2009

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http://ec.europa.eu/health/ph_risk/committees/04_scenihr/scenihr_memberswg_en.htm

ABSTRACT

This Opinion addresses the issue of whether the replacement of mercury-containing, blood-pressure measuring devices (sphygmomanometers) would (i) endanger proper health care including specific groups of patients, and/or (ii) compromise long-term translational epidemiological studies for public health. In addition, the availability and quality of alternative devices for blood pressure measurements have been considered. Blood pressure measurement is vital for the prevention and treatment of blood pressure related diseases, and for monitoring of cardiovascular homeostasis. Based on long-term experience, blood pressure measurement using the mercury sphygmomanometer is currently regarded as the gold standard method for indirect measurement of blood pressure.

Alternative devices are gradually replacing the mercury sphygmomanometer. Mercury-free sphygmomanometers which use auscultation for the determination of blood pressure have the same limitations as mercury sphygmomanometers. These limitations result from poor observer technique and/or bias and may be avoided by using automated oscillometric devices which operate under a different principle from auscultation. Although they all employ the same oscillometric principle, each oscillometric device follows a manufacturer-specific algorithm which requires individual assessment for technical accuracy and clinical validation. Accurate blood pressure measurements with automated oscillometric sphygmomanometers are possible, although they have limitations in certain patient groups. Clinical validation in these specific groups of patients is required before oscillometric devices can be used safely. For certain patient groups, blood pressure measurement by a trained observer, using mercury sphygmomanometers or a validated auscultatory alternative, remains the most accurate and reliable form of indirect blood pressure measurement. It is emphasised that all alternative devices require metrological verification and clinical validation.

For all blood pressure measurement devices, including mercury sphygmomanometers, regular maintenance is of utmost importance. For the alternative blood-pressure measuring devices, a regular metrological verification is needed to ensure the accuracy of the measurements. The metrological verification does not necessarily require the use of mercury sphygmomanometers. However, it is recommended that mercury sphygmomanometers remain available as a reference standard for clinical validation of existing and future mercury-free blood-pressure measurement devices. Therefore, the mercury sphygmomanometer should remain available as a reference standard until an alternative device is developed and recognised as such.

Keywords:

SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks, Mercury, Cardiology, Epidemiology, Public health, Blood pressure, Hypertension, Arrhythmia, Diabetes, Pre-eclampsia, Mercury sphygmomanometers, Aneroid sphygmomanometers, Oscillometric sphygmomanometers, Electronic sphygmomanometers, Mercury-free sphygmomanometers.

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EXECUTIVE SUMMARY

Mercury and its compounds are highly toxic to humans, ecosystems and wildlife. Mercury can exist in several chemical forms (Hg^0 , Hg^{1+} , Hg^{2+}), each with its own toxicological profile. In general terms, the toxicity of these chemical forms is highest for the organic mercury compounds, followed by elemental mercury and inorganic mercury compounds. A Community Strategy Concerning Mercury was adopted in January 2005 with the key aim of reducing mercury levels in the environment and reducing human exposure. The replacement of mercury-containing blood-pressure measuring devices (sphygmomanometers) by alternative mercury-free devices raises the issue whether this would

- (i) endanger proper health care including specific groups of patients, and/or
- (ii) compromise long-term translational epidemiological studies for public health.

In addition, the availability and quality of alternative devices for blood pressure measurements needs to be considered.

The blood pressure measurement is vital for the prevention and treatment of blood pressure related diseases, and for monitoring cardiovascular homeostasis. The indirect measurement of blood pressure with mercury sphygmomanometers has identified arterial hypertension as a major risk factor for cardiovascular diseases. In addition to the use in clinical settings, the mercury sphygmomanometer is also used in long-term epidemiological/observational studies on cardiovascular disease development. A change in population blood pressure has a direct effect on the morbidity and mortality of cardiovascular diseases. Based on long-term experience, blood pressure measurement using the mercury sphygmomanometer is regarded as the gold standard method for indirect measurement of blood pressure. The use of the mercury sphygmomanometer has practical and technical limitations, and requires specific training. In addition, there should be a special emphasis on regular maintenance of the mercury sphygmomanometer in order to maintain its accuracy. When blood pressure is measured by a trained observer using the auscultatory technique, the mercury sphygmomanometer currently remains the most accurate device for indirect blood pressure measurement.

The mercury column functions as a pressure sensing and displaying component, so it seems likely that this can be replaced by a mercury-free manometer. Indeed, mercury-free alternatives for pressure measurement are commercially available such as the aneroid manometer and the electronic pressure transducer. These alternative sphygmomanometers use auscultation for determination of the blood pressure, and therefore, have the advantages and limitations (such as the observer performance) which also apply to the mercury sphygmomanometer, and are characteristic of the auscultatory technique. The auscultation method is based on the observation of the recurrence of the blood flow in the occluded artery (using a cuff) of the upper arm by listening to the sounds generated by the recurrent blood flow and disappearance of the sounds when the occlusion is completely removed (by dilation of the cuff), and normal blood flow is restored. In addition, there are non-auscultatory, mercury-free devices available which use the oscillometric technique to measure blood pressure based on changes in arterial pulsation during cuff inflation/deflation. Oscillometric instruments operate under a completely different principle and are thus not considered as true "alternatives" to Hg sphygmomanometers.

The various alternatives have widely varying levels of accuracy, emphasising the importance of clinical validation. Regular maintenance is of the utmost importance for proper functioning of all measurement instruments. Even validated oscillometric devices may have accuracy limitations in special patient groups, including patients with arrhythmias, diabetes, pre-eclampsia, and the elderly. These limitations do not apply to devices using the auscultatory technique. Therefore, validated non-mercury auscultatory alternatives are appropriate for these patients. For alternative blood pressure measurement devices, a metrological verification is needed to ensure the accuracy of the

measurements. Mercury sphygmomanometers are not essential as reference devices for this metrological verification (calibration). In addition, an independent device accuracy assessment is recommended to evaluate the clinical performance. Various clinical validation protocols are available to assess the accuracy of automated alternative devices against mercury sphygmomanometers.

The mercury sphygmomanometer is gradually disappearing from clinical use. Mercury-free blood pressure measuring devices (when clinically validated) are generally reliable substitutes for mercury-containing sphygmomanometers in routine clinical practice. These alternative devices include both auscultatory devices requiring a trained observer and automated oscillometric devices for which some instruction is needed. Clinically validated, auscultatory mercury-free devices are equivalent to mercury sphygmomanometers, and are thus suitable for specific groups of patients, including patients with arrhythmias, diabetes, pre-eclampsia and the elderly. The alternative devices using auscultation have similar limitations as the mercury sphygmomanometers regarding the observer technique and bias associated with auscultation itself. These may be avoided by using automated oscillometric devices, which, when properly validated, allow accurate blood pressure measurements. The oscillometric technique has mainly been clinically validated in adult populations including a wide range of blood pressures but not in a wide range of ages and clinical conditions, and should not be used in some specific clinical conditions including pre-eclampsia. There is no evidence of adverse effects on patients' health in clinical settings due to the replacement of mercury-containing sphygmomanometers by validated mercury-free alternatives. There are adequate alternatives in most clinical conditions/settings. In special conditions, such as pre-eclampsia, mercury-free auscultatory devices should be preferred until further validation of oscillometric devices.

In conclusion, when blood pressure is measured by a trained observer using the auscultatory technique, the mercury sphygmomanometer or a validated auscultatory alternative currently remains the most accurate instrument for indirect blood pressure measurement, especially for certain patient groups. For all blood-pressure measuring devices, regular maintenance is of primary importance. In order to maintain a high-level quality of blood pressure measurements it is recommended that mercury sphygmomanometers remain available as reference standards for clinical validation studies of existing and future non-mercury-containing blood-pressure measurement devices. For on-going, long-term, epidemiological studies currently using mercury sphygmomanometers it is advisable not to change the method of measurement. Therefore, it will be necessary to keep mercury sphygmomanometers available in order to compare them with the alternatives in these studies. It is emphasised that mercury devices should remain available as reference standards until an alternative standard is developed and recognised.

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1. BACKGROUND

Directive 2007/51/EC¹ (point 3 of entry 19a on mercury) requires that, “the Commission shall carry out a review of the availability of reliable safer alternatives that are technically and economically feasible for mercury containing sphygmomanometers and other measuring devices in healthcare and in other professional and industrial uses”.

The sale of all mercury containing measuring devices to the general public has been banned under Directive 2007/51/EC with effect from 3 April 2009 due to concerns about the risks posed to human health from discharges of mercury to the environment from broken or discarded measuring devices. However, sphygmomanometers in healthcare were exempted as these devices were regarded by many Member States as essential for the diagnosis of certain life-threatening diseases such as arrhythmia, accelerated hypertension, as well as in gynaecology and obstetrics. The exemption also applies to other measuring devices in healthcare. That position was also in line with the consensus of opinion among the Member State experts of the Commission’s Working Group on Medical Devices.

Nevertheless, the European Parliament and the Council decided during the co-decision procedure that the Commission should review the issue by 3 October 2009.

Since March 2008, The Directorate-General (DG) for Enterprise and Industry of the European Commission has been preparing for the review by addressing questionnaires to various stakeholders (Member States, non-governmental organizations, scientific organisations, and industry) in order to collect relevant information. In addition, the positions of stakeholders on mercury-containing sphygmomanometers (and the existence of alternatives) have been recorded in discussions which have taken place during the meetings of the Limitation Working Group which is responsible for the implementation of Directive 76/769/EEC.

Considering the critical importance of the health and safety of patients, DG Enterprise would like to request an opinion of SCENIHR as crucial input for the Commission’s review. The Commission needs to ensure a careful examination of the available scientific and clinical evidence, so that any future action, if required, would achieve a good balance between protection of human health from adverse effects of mercury through the environment for the population in general, and protection of the health of patients requiring accurate blood pressure measurement.

¹ Available at: http://ec.europa.eu/enterprise/chemicals/legislation/markrestr/amendments_en.htm

2. TERMS OF REFERENCE

SCENIHR is requested to review the provided material and any further documentation available, and to specifically answer the following questions:

- (1) Is there sufficient evidence to demonstrate that mercury-free blood pressure measuring devices such as aneroid or electronic instruments are *generally reliable* substitutes for mercury-containing sphygmomanometers?²
- (2) Have mercury-free sphygmomanometers been adequately validated over a *wide range* of blood pressures, ages, and clinical conditions to allow for routine use in hospitals and outpatient settings?
- (3) Have mercury-free sphygmomanometers been adequately validated for the diagnosis of hypertension in *specific clinical conditions* such as arrhythmia, pre-eclampsia in obstetrics and certain vascular diseases?
- (4) Are mercury-based sphygmomanometers essential as reference devices for *validation* of long-term clinical epidemiological studies enrolling patients with hypertension?
- (5) Are mercury-based sphygmomanometers essential as reference devices for *calibration* of the mercury-free sphygmomanometers when the latter are used for routine diagnostic purposes?
- (6) Is SCENIHR aware of any *adverse effects* for patients' health due to the replacement of mercury-containing sphygmomanometers by mercury-free alternatives?

² Substitutes cover both liquids to replace mercury in manometers and other measurement techniques based on different technologies, such as electronic devices. The term "*reliable* substitutes" denotes devices that perform (in comparison with the mercury-based sphygmomanometers) to equal or greater accuracy when maintained and used correctly, also taking into account error statistics where known (such as error rates and the magnitude of errors) and the intervals between maintenance and recalibration.

3. SCIENTIFIC RATIONALE

3.1. Introduction

Mercury and its compounds are highly toxic to humans, ecosystems and wildlife. Therefore, the Community Strategy Concerning Mercury was adopted in January 2005 with the key aim of reducing mercury levels in the environment and to reducing human exposure.

This Opinion addresses the issue of whether the replacement of mercury-containing, blood-pressure measuring devices (sphygmomanometers) would (i) endanger proper health care including health care for specific groups of patients, and/or (ii) compromise long-term translational epidemiological studies for public health. For this purpose the availability and quality of alternative methods for blood pressure measurements have been evaluated.

3.2. Methodology

For this Opinion, evidence from a wide variety of sources, including peer-reviewed scientific and medical literature and published reports of institutional, professional, governmental and non-governmental organisations has been considered. In accordance with the practice of SCENIHR and its Working Groups, no reliance has been placed on unpublished work or publicly available opinions that are not scientifically based. Single case or anecdotal reports were generally not considered in establishing this Opinion. To review as much evidence as possible, especially where the available data are limited, attention has been given to some less rigorous studies where no other information was available. During the course of the deliberations and drafting the document, a Call for Information was issued by the Commission and the submissions have all been considered.

3.3. Mercury Toxicity

As previously described in the Opinion of SCENIHR on the use of dental amalgam (SCENIHR 2008), mercury is a metallic element that occurs naturally and also in the form of several types of ore, the mercury burden of the environment being derived predominantly from natural sources. Input into the earth's atmosphere occurs regularly through emissions from volcanoes, soil erosion and the combustion of fossil fuels. Widespread utilisation of mercury and its compounds in a number of industries over the last several centuries has resulted in the release of large amounts of mercury into the atmosphere, increasing the total amount in the ecosphere. Of special importance has been the accumulation of some mercury compounds in the aquatic food chain and the use of mercury compounds in a variety of medical and cosmetic products including dental amalgam (SCENIHR 2008).

It is also important to note that there are several different forms of mercury. First, there is elemental mercury itself, a volatile form of the liquid metal, referred to as Hg^0 . Second, mercury is stable in two other oxidation states (Hg^{1+} and Hg^{2+}) and is able to form inorganic compounds, of either monovalent or divalent form, including mercuric chloride (HgCl_2), mercurous chloride (Hg_2Cl_2), mercuric sulphide (HgS), and mercuric selenide (HgSe). Third, mercury is able to form a variety of organic compounds, including methylmercury. There is a clear connection between all these forms with respect to the global cycle of mercury (Nielsen et al. 2006). Elemental mercury may be converted to soluble inorganic forms, which may be methylated in water, especially by microorganisms, and which enter the food-chain and accumulate in the tissues of large

predatory fish. The ratio of methylmercury in these fish to the mercury concentration in the water can be as high as 105.

Due to the widespread use of mercury in industrial settings, a large and detailed database on human effects of elemental mercury inhalation is available. A number of reviews addressing the toxicity of elemental mercury have been published (ATSDR 1999, BAT 1997, IRIS 2002, MAK 1999, UNEP 2002). Each form of mercury has its own toxicological profile, although, in general terms, the organic mercury compounds have the highest toxicity, followed by elemental mercury and inorganic mercury compounds. This is important when considering different exposure routes to these forms. Elemental liquid mercury is used in measuring devices such as sphygmomanometers, and previously thermometers.

The assessment of elemental mercury toxicity is mainly based on observations in occupationally exposed humans. Inhalation of extremely high concentrations of elemental mercury, in excess of 10 mg/m^3 , may produce bronchitis and pneumonia, in addition to symptoms of the central nervous system. After long-term elemental mercury exposure in occupational settings and under occupational hygiene conditions considered as poor by present standards, the major effects of elemental mercury reported are on the central nervous system. The major manifestations of mercury poisoning from inhalation of elemental mercury are increased excitability and tremors. Characteristic symptoms after long-term high dose exposures (the inhalation of concentrations above 0.5 mg/m^3 for many years) are muscle tremors in fingers, eye lids and lips, which may progress to chronic spasms of the extremities. After chronic occupational exposure to mercury vapour, proteinuria and even a nephritic syndrome have been described in humans. The glomerular damage may progress to interstitial immune-complex nephritis. Gingivitis and hypersalivation with a strong metallic taste are considered to be further symptoms of chronic inhalation exposure to elemental mercury.

Occupational allergies to mercury were rare, even with widespread exposures to elemental mercury at the workplace and the use of mercury in medicinal preparations (including the use of Hg^{2+} due to its bactericidal activity) and consumer products (Kanerva et al. 1993).

Mercury is a serious non-degradable environmental pollutant, which eventually accumulates on the sea bed and contaminates marine life (Langford and Ferner 1999). After discharge in the environment, natural transformations and environmental pathways of mercury are very complex and greatly affected by local conditions. There are two main types of reactions in the mercury cycle that convert this metal into its various forms: oxidation-reduction and methylation-demethylation. In oxidation-reduction reactions, mercury is changed from the relatively inert Hg^0 to the more reactive Hg^{2+} . The oxidation of elemental mercury Hg^0 in the atmosphere is an important mechanism involved in the deposition of mercury on land and water. Hg^0 can volatilize relatively easily and be transported in the atmosphere. In contrast Hg^{2+} has a short atmospheric residence time due to its solubility in water, low volatility and reactive properties. Hence after this conversion, mercury can be rapidly taken up in rain water or adsorbed onto small particles and be subsequently deposited in the environment (Nielsen et al. 2006).

In the environment mercury is transformed into methyl mercury when the oxidized, or mercuric species (Hg^{2+}) gains a methyl group ($-\text{CH}_3$). This methylation is primarily a natural, biological process resulting in the production of highly toxic and bioaccumulative methylmercury compounds (MeHg^+) that build up in living tissues and increase in concentration in the food chain from microorganisms like plankton to fish and humans. Rates of biomethylation are a function of environmental variables affecting ion availability as well as the population sizes of methylating microbes and pH (acidic conditions are more favourable).

Humans are exposed to methylmercury almost entirely by eating contaminated fish, seafood and wildlife that are at the top of the aquatic food chain.

3.4. Blood Pressure Measurements

3.4.1. General information

Raised blood pressure throughout its range is the most significant cause of death and disability in the world (Lopez et al. 2006). Accurate blood pressure measurement is therefore vital in the prevention and treatment of blood-pressure-related diseases. Additionally, in very ill patients, accurate measurement of blood pressure is essential for monitoring cardiovascular homeostasis.

For more than a century, blood pressure has been measured worldwide both in clinical practice and medical research by auscultation using the mercury sphygmomanometer. Riva-Rocci described this indirect measurement of the blood pressure as the outside pressure needed to occlude the brachial artery (Riva-Rocci 1896). This was achieved by wrapping an inflatable bladder encased in a non distensible cuff, around the arm or leg and inflating it until the pressure on the cuff is greater than the blood pressure in the artery, and the artery is occluded. The cuff is then slowly deflated until the palpable pressure reappears through the partially compressed artery. The level of pressure on the bladder which is reflected on the manometer at the time the first repetitive sound is heard, is the maximum pressure generated during each cardiac cycle. This is defined as systolic blood pressure. The diastolic blood pressure is the level of pressure at which sounds disappear completely when the artery is not compressed and blood flow is restored. In 1905 Korotkov described the auscultatory method; this is the observation of the repetitive sounds generated by the blood flow (Korotkov 1905). As the cuff pressure reduces gradually during the deflation the Korotkov sound changes in intensity and quality, and five different stages can be distinguished (Korotkov 1905).

The indirect blood pressure measurement with mercury sphygmomanometers has been shown to be valuable in several clinical circumstances. Their extensive use has allowed the collection of the necessary evidence to identify arterial hypertension as a major risk factor for cardiovascular diseases. Most epidemiological and clinical data on hypertension as a cardio-vascular risk factor have been obtained by this blood pressure measuring device. Based on this relation to clinical disease and long-lasting experience, blood pressure measurement using the mercury sphygmomanometer currently is regarded as the gold standard method for indirect measurement of blood pressure.

3.4.2. Factors affecting blood pressure measurement

It is important to be aware of the factors that affect blood pressure measurement (Rose 1965):

- (1) The technical skills of the observer;
- (2) The inherent variability of blood pressure;
- (3) The accuracy of the device, including its limitations and applications;
- (4) The difficulty in measuring blood pressure in some special groups, e.g. the elderly, patients with arrhythmias, patients with a large arm, children, pregnant women.

The most important element in using auscultatory methods is the observer. All observers need adequate training in listening and recognising the correct sounds. Most common sources of error in many reports are mostly due to the observer, including poor hearing, difficulty/failure in interpreting the Korotkov sounds and lack of concentration. Most serious errors involve the interpretation of the Korotkov sounds and recognising diastolic pressure. Observers may be influenced by the subjects. For example, observers tend to be reluctant in diagnosing young healthy subjects as hypertensive or obese older persons as normotensive when the blood pressure is around 140/90 mmHg (systolic/diastolic blood pressure) resulting in a tendency to under read in the first case and over estimate in the latter. Observer-related issues include: prejudice and bias such as threshold avoidance; terminal digit preference; fast deflation, etc. (Beevers et al. 2001).

To accurately measure blood pressure, the following important criteria have to be applied, irrespective of what type of device is being used.

- Posture of the patient supine, sitting or standing.
- Cuff at heart level and arm supported; if not supported, isometric exercise is performed and will result in recording a higher blood pressure.
- The use of correct cuff and bladder size for the appropriate arm/leg size. Over cuffing (use of a bladder that is too large) will lead to under estimation of blood pressure, and under cuffing (use of a bladder that is too small) will over estimate the blood pressure.
- Measurement of the blood pressure on both arms at first visit to help identify consistent difference in blood pressure between the arms.
- Accuracy of the device; the device should be well maintained, in pristine condition, calibrated as per the manufacturer's instructions and validated according to accepted standards using appropriate protocols.

3.4.3. Blood pressure measurements in routine clinical practice

Repeated office blood pressure measurements are mandatory in clinical practice to characterise precisely the blood-pressure-related cardiovascular risk of individual subjects. Precise recommendations are available to ensure standardised accurate measurements (O'Brien et al. 2003, Parati et al. 2008a), which until now have been obtained in most cases through the auscultatory technique making use of mercury or aneroid sphygmomanometers. Given the fact that aneroid manometers easily lose calibration, mercury manometers have been, until now, the recommended tools for auscultatory blood pressure readings, on which the conventional management of hypertensive patients has been based over the last 60-70 years. In more recent years an increasing use of home blood pressure monitoring and 24-hour ambulatory blood pressure monitoring has been observed (both based on oscillometric blood pressure measurements), aimed at complementing the information provided by office blood pressure measurements. This is based on the evidence of a stronger prognostic value of 24-hour ambulatory and home blood pressure monitoring as compared to isolated office readings (Parati et al. 2008b, Parati et al. 2009b, Verdecchia et al. 2009). A slow progressive increase in the use of oscillometric blood pressure measuring devices at the time of the office visit has been recently observed, although auscultatory readings are still preferred by physicians in most countries.

There are a number of physiological and pathological states that may influence the ability of an oscillometric device to obtain an equivalent reading to a mercury sphygmomanometer. Oscillometric measurements are dependant on movement, and changes in the amplitude of this movement, in the artery, and therefore maybe altered. Oscillometric measurements cannot be relied on in patients with arrhythmias, or some valvular heart disease such as aortic incompetence. Other patients with altered vascular compliance, such as diabetics, or the elderly, could have less accurate blood pressure readings using oscillometric measurement. Changes in vascular compliance may also be confounded by oedema, intravascular volume, hyperdynamic circulation and by changes in cardiac output such as pre-eclampsia, in which oscillometric readings frequently underestimate the blood pressure (Shennan and De Greeff 2007). Although the accuracy and reproducibility of Korotkov sounds in these disease states are not known, listening to the Korotkov sounds remains the technique in which current knowledge of indirect blood pressure is determined, and therefore, the auscultatory method of blood pressure is recommended in such populations.

3.4.4. Blood pressure measurements in epidemiological / observational studies

Very comprehensive research on population blood pressure exists throughout the world. These studies are essential for defining hypertension prevalence, awareness and treatment in any geographical region/country. A change in population blood pressure of 2 mmHg in systolic blood pressure translates to a change in stroke mortality of ten percent and coronary heart disease mortality of seven percent (Lewington et al. 2002). Therefore, data on progression from normotension to prehypertension and hypertension are very important in epidemiological research. The data have documented that prehypertension carries an increased risk for cardiovascular morbidity and mortality, and a high risk for progression to sustained hypertension (Hansen et al. 2007a, Julius et al. 2006). In this respect, changes from normotension to prehypertension are as important as the observation of hypertension itself. Reliable data are heavily dependent on blood pressure measurements carried out meticulously by properly trained personnel and with precise equipment. For this, adherence to a standardised technique over time is crucial. Findings of changes in population blood pressure are only meaningful if they are ascertained to be true differences and not related to a change in methods applied.

Nearly all results on population blood pressure have been obtained by the use of a standard mercury sphygmomanometer by well-trained health personnel (Cutler et al. 2008). Despite this, the readings are not without observer bias and end-digit preference. In an attempt to minimise observer bias and end-digit preference, a number of highly recognized epidemiological research institutions have used the Random Zero Mercury Sphygmomanometer, where the reader has to subtract a random chosen magnitude of mmHg (from 0 to 20 mmHg) at the very end of the measurement. Despite minimising observer bias, the equipment has been shown to slightly underestimate the "true" blood pressure level as obtained by the use of a standard mercury manometer (Yang et al. 2008). Another approach that has been employed is the "London School of Hygiene Sphygmomanometer" (Andersen and Jensen 2007) where the reader is blinded to the mercury column but has to tap a button when they hear the first and the fourth Korotkov sounds (phase 1 and phase 5).

In recent years, 24-hour ambulatory blood pressure measurements have been introduced in population studies and comprehensive databases have been constructed, e.g. the Idaco Database on population studies with contributions from many parts of the world (Hansen et al. 2007b). All these studies have convincingly shown that 24-hour ambulatory blood pressure measurements determined with oscillometric devices (at approximately 80 readings over 24 hours), are superior for prediction of cardiovascular morbidity and mortality as compared to a few measurements of blood pressure performed in clinical conditions with a standard mercury sphygmomanometer. In almost all these studies, although not exclusively, the comparator has been the standard mercury sphygmomanometer (Hansen et al. 2007b).

Research into normal values for home blood pressure and the prognostic implication is less comprehensive. This research has been almost exclusively carried out with automatic oscillometric devices, with measurements being compared to the mercury sphygmomanometer. Data are accumulating showing that the predictive prognostic value of a certain number of home blood pressure readings is superior to a single or a few blood pressure readings performed in a clinic using a mercury sphygmomanometer (Sega et al. 2005). The home readings are a reflection of more precise estimation of the actual blood pressure levels over many readings as compared to few readings in the clinical setting. So far, comparisons of measurements obtained with mercury sphygmomanometer versus oscillometric automatic devices, obtained in the same clinical setting for determination of population blood pressure and prognostic implications, are missing. However, in the Pamela Study, three clinic readings with a mercury sphygmomanometer were compared to two home blood pressure oscillometric readings (Sega et al. 2005). As expected, the clinical readings were somewhat higher, but the prognostic implication was not that much different.

In long-term outcome clinical trials, usually running for three to five years, mercury sphygmomanometers have been used as the gold standard for office blood pressure measurement. In some recent trials (the HOT Study, the ASCOT Study and the OnTarget Study) automatic oscillometric devices were used (Dahlöf et al. 2005, Hansson et al. 1998, Yusuf et al. 2008). In some of these studies it was shown that small differences in measured blood pressure already can have an impact on cardiovascular diseases.

There is rapidly growing information on normal values and the prognostic implications of 24 hour ambulatory blood pressure measurements with oscillometric devices, while knowledge on self/home blood pressure measurements with oscillometric devices is less substantial. So far, a direct comparison between clinic blood pressure and prognostic implication based on measurements carried out with mercury sphygmomanometer and those with automatic oscillometric devices is lacking.

In conclusion, the vast majority of information on population blood pressure (secular trends, progression to hypertension and prognostic implications, and also the benefits from treatment-induced blood pressure reduction in terms of cardiovascular events prevention) has so far been obtained with the use of mercury sphygmomanometers. Reliable data on changes in population blood pressure level, incidence and prevalence of hypertension, awareness and treatment, derived from follow-up studies are dependent on the use of consistent and trustworthy methods. It can be expected that epidemiological/observational studies in the future will comprise repetitive blood pressure measurements at home carried out with well-calibrated, well-validated automatic oscillometric equipment. For the moment, mercury sphygmomanometers are essential for such validation of newly developed blood pressure measurement devices. Otherwise, the conclusions based on the results of long-term epidemiological studies on changes in population blood pressure may be seriously jeopardised.

3.5. Mercury sphygmomanometers

The mercury-containing sphygmomanometer should not be viewed as an absolute standard. It is however, with all its faults as an indirect blood pressure determination, the method used to establish our current knowledge. Since Riva-Rocci's times mercury sphygmomanometers associated with the occlusion-auscultatory technique have been used in clinical and epidemiological studies on hypertension. They represent the cornerstone for cardiovascular disease prognosis and prevention, as well as in the daily clinical management of patients with high blood pressure. As a result of this time-honoured use, blood pressure values are still quantified in mmHg both in current practice and in research, and doctors keep watching the mercury column as the most faithful indicator of the blood pressure levels in their patients. A commonly perceived advantage of mercury manometers lies in the fact that, when they are well maintained (see below), they offer "absolute" measurements of blood pressure, and represent a "gold standard" reference technique used to validate all other methods which provide information on blood pressure levels in mmHg without using a mercury column. The blood pressure measurement based on the mercury sphygmomanometer is an indirect blood pressure determination, and is difficult to perfectly mimic with other techniques unrelated to auscultation of Korotkov sounds.

3.5.1. Characteristics

The high-density of liquid mercury metal provides an acceptable short length of the rising column for visualization of the pressure in the cuff. Therefore, the mercury column in a sphygmomanometer is used as a simple, gravity-based unit. When properly maintained and serviced and when used by knowledgeable trained health professionals, it can give accurate indirect measurements of both systolic and diastolic pressure. Currently it is considered to be the most accurate technique (O'Brien et al. 2003).

A complete mercury sphygmomanometer requires a cuff, bladder, tubing and a rubber bulb, and should be maintained in good condition and serviced regularly according to the manufacturers' instructions. Mercury sphygmomanometers are easily checked and maintained, but great care should be taken when handling mercury. The revised European Standard (EN 1060 series) recommends that mercury sphygmomanometers display a warning to this effect (CEN 1995a).

3.5.2. Limitations

Despite its widespread availability for almost a century, there can be major problems with the use of mercury sphygmomanometers in clinical practice. Reports from hospitals and family practices have suggested that many mercury sphygmomanometers are defective because of poor maintenance (Beevers and Morgan 1993, Burke et al. 1982, Feher et al. 1992, Gillespie and Curzio 1998, Hutchinson et al. 1994, Markandu et al. 2000, Wingfield et al. 1996).

Moreover, several studies have shown that there is a lack of knowledge of the technical aspects of the actual blood pressure measurement in both doctors and nurses and other health care professionals who use the mercury sphygmomanometers. The reports also suggest that the technique of blood pressure measurement is not applied very well. Additionally, there is a lack of knowledge of the appropriate blood pressure equipment and how to maintain the devices so that they are calibrated and in pristine condition. One should be aware of the fact that issues of maintenance are a factor for every blood pressure measurement device.

There are several other limitations of using the auscultatory method which affect both mercury and aneroid manometers:

- Terminal digit preference: Tendency of the observer to round off the number to their choosing e.g. 144/96 mmHg as 140/100 mmHg or 150/90 mmHg (systolic/diastolic blood pressure). This is the zero preference. The observer finds it easier to read the prominent larger 10 mmHg markings instead of the smaller, 2 mmHg markings.
- Errors may occur when the manometer is not kept vertical (see fig. 1), and the device is rested on the side of the bed or, having it tilted against the pillow. This is an issue when the device is being used at the patient's bedside, not when used for public-health monitoring.

Positioning of the Hg manometer

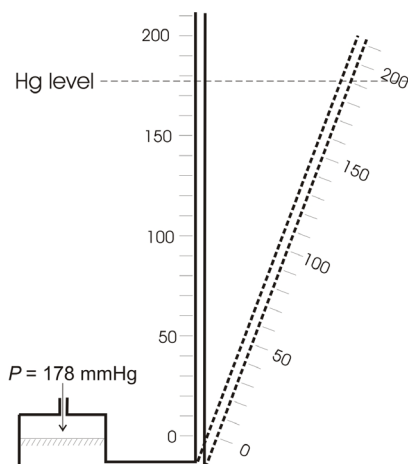


Figure 1: Measurement error due to incorrect positioning of the Hg manometer. In this diagram the incorrect positioning of the tube results in a measurement error of ca. 12 mmHg.

- Inflation/deflation system:

Another important limitation to consider is the performance of the inflation/deflation system and of the occluding bladder encased in a cuff, and proper application of auscultation with a stethoscope. Those issues apply to all blood pressure measuring devices using the auscultatory method.

The inflation/deflation system consists of an inflating and deflating mechanism connected by rubber tubing to an occluding bladder. The standard mercury sphygmomanometers used in clinical practice are operated manually, with inflation being effected by means of a bulb compressed by hand and deflation by means of a release valve, which is also controlled by hand. The pump and control valve are connected to the inflatable bladder and thence to the sphygmomanometer by rubber tubing. Leaks from cracked or perished rubber make accurate measurement of blood pressure difficult because the fall of the mercury cannot be controlled. The length of tubing between the cuff and the manometer should be at least 70 cm and that between the inflation source and the cuff should be at least 30 cm. Connections should be airtight and easily disconnected.

In addition, technical (maintenance) problems may exist such as:

- (i) Oxidisation of the mercury is another very common occurrence, which can increase with time and make the columns difficult to read.
- (ii) The markings on the column also fade with time, again making it impossible to read accurately.
- (iii) Dynamic response, see 3.5.3.

3.5.3. Technical accuracy of Hg sphygmomanometers

The mercury manometers incorporate the (non SI unit) mmHg as a read-out system. The use of this manometer does not automatically guarantee that the cuff pressure measurement is always correct. In 1952, the Physikalisch-Technische Bundesanstalt in Germany issued requirements for these sphygmomanometers on a voluntary basis. The International Organisation of Legal Metrology published its first International Recommendation (IR 16) in 1973 and at approximately the same time national standards and similar documents were published in several countries such as the USA and Switzerland. Since then, these documents have been updated several times. To support the "Council Directive 93/42/EEC concerning medical devices" the European standards organisation CEN developed a standard (EN 1060, part 1-4) between 1995 and 2004 (CEN 1995a, 1995b, 1997, 2004), which became a harmonized standard in that framework. Recently the international standard organisations ISO and IEC jointly developed standards to test sphygmomanometers; they were published between 2007 and 2009 (IEC 2009, ISO 2007). These standards are expected to replace the CEN standards in the near future.

Regarding the accuracy of Hg manometer there are three main aspects to be considered:

- positioning of the Hg manometer (see above)
- dynamic response of the Hg column (see below)
- clearness of the display (see above)

Since the technical accuracy of the Hg manometer is affected by the inclination relative to gravity, means need to be provided to ensure the correct positioning of the reservoir and the tube, e.g. a water-level. Figure 1 illustrates the effect of incorrect positioning on the accuracy. According to ISO 81060-1 (ISO, 2007) a portable Hg manometer "shall be provided with an adjusting or locking mechanism to secure it in the position for use as indicated in the accompanying documents".

Dynamic response of the Hg column

To prevent the spillage of Hg the ISO 81060-1 standard requires the following:

The Hg manometer shall incorporate a stopping device at the top of the tube that

- permits both the inward and outward flow of air, and
- prevents the passage of liquid mercury.

The reservoir shall also be fitted with a stopping device to prevent the Hg from flowing out of the reservoir neck and into the attached tubing and permits the inward and outward flow of air.

When the passage of air is limited owing to contamination or deterioration of the stopping devices, the falling pressure is displayed with some delay by the mercury column in the tube. This delay prevents the user from reading the correct pressure value; when measuring during cuff pressure deflation, there will be a systematic error resulting in too high blood pressure values.

Consequently the metrological test of a Hg manometer has to include

- the accuracy of the static pressure display, checked in pressure steps not greater than 50 mmHg;
- the dynamic response by a rapid pressure change; and
- the clearness of the tube by visual inspection.

The following list summarises the technical features determining the accuracy of mercury sphygmomanometers (O'Brien et al. 2003).

Features affecting accuracy of the mercury sphygmomanometer:

- The top of the mercury meniscus should rest at exactly zero without pressure applied; if it is below, add mercury.
- The scale should be clearly calibrated in 2 mm divisions from 0 to 300 mmHg and should indicate accurately the differences between the levels of mercury in the tube and in the reservoir.
- The diameter of the reservoir must be at least ten times that of the vertical tube, or the vertical scale must correct for the drop in the mercury level in the reservoir as the column rises.
- Substantial errors may occur if the manometer is not kept vertical during measurement. Calibrations on floor models are especially adjusted to compensate for the tilt in the face of the gauge. Stand-mounted manometers are recommended for hospital use. This allows the observer to adjust the level of the sphygmomanometer and to perform measurement without having to balance the sphygmomanometer precariously on the side of the bed.
- The air vent at the top of the manometer must be kept patent, as clogging will cause the mercury column to respond sluggishly and to overestimate pressure.
- The control valve is one of the most common causes of error in sphygmomanometers and when it becomes defective it should be replaced. Spare control valves should be available in hospitals and a spare control valve should be supplied with sphygmomanometers.

3.6. Technical aspects of the alternatives to Hg sphygmomanometers

The Korotkov sounds in the artery may be detected by auscultation which may be performed either manually (by the observer) or automatically (by electronic equipment). Since the Hg manometer is only the pressure sensing and displaying component in the occluding cuff technique, other manometers can be used instead. Although a lot of different pressure measuring techniques are conceivable, the following two are applied in sphygmomanometers:

- An aneroid manometer with an analogue display (circular scale with a pointer) and
- An electrical pressure transducer with analogue look, but digital display.

In addition to the alternative devices using auscultation, there also exists the oscillometric technique which does not use auscultation, but instead uses the oscillation in the cuff pressure due to the pulsation in the artery.

3.6.1. Auscultatory mercury-free sphygmomanometers

3.6.1.1 Non-automated auscultatory devices

Sphygmomanometers using aneroid (or mechanical) gauges (based on an elastic pressure sensing element) are common alternatives to Hg sphygmomanometers. The aneroid machines do not use liquid to display the information about the estimated values for the blood pressure levels.

ANEROID sphygmomanometers have been available for probably as long as the mercury manometer. They are commonly used for handheld sphygmomanometers, but are also available for portable or wall-mounted sphygmomanometers. The reliability of the aneroid manometer is affected by the technical design of the device and the quality of its production to a much greater extent than the mercury manometer. As one example, the long-time stability (reproducibility) of the aneroid manometer requires a pre-aging of the elastic pressure sensing element.

Another important issue is the sensitivity to mechanical shock. A simple standard aneroid manometer will not usually withstand drops from the table or heavy strokes. Since this is not acceptable in daily life the ISO/IEC Joint Working Group was the first to introduce requirements on mechanical strength for portable and handheld aneroid manometers. With the exception of stationary non-automated sphygmomanometers, including the aneroid type, all devices must function normally following a free fall from 25 cm. Additional requirements exist for all non-automated sphygmomanometers, including the aneroid type when they are labelled "Shock Resistant"; these must withstand drops from 1 m without the loss of performance. Devices following the requirements of ISO 81060-1, especially those labelled "Shock Resistant", will be robust enough for normal handling.

However, there are some reservations about the maintenance of the mechanical parts of the aneroid machine (Coleman et al. 2005). Other limitations with auscultation are similar to those with mercury manometer.

ELECTRONIC devices translate the pressure in the cuff into analogue-like or numerical display. The Hg column is simulated by a LCD (or LED), or there is a numerical display, or the pointer of the aneroid gauge is simulated by LEDs (Graves et al. 2004, Stergiou et al. 2008a).

These devices measure the pressure of the cuff with an electrical transducer similar to an automated sphygmomanometer. Regarding the pressure measurement, these devices follow the requirements for automated sphygmomanometers. A disadvantage of these devices is that electrical power is required.

3.6.1.2 Automated auscultatory devices

The first automated sphygmomanometers became available in the 1970s. These devices were designed to replace the observer and their stethoscope with a microphone and some analogue electronics. The microphone is placed in a small pocket in the cuff. The analogue electronics amplifies and filters the Korotkov sound detected by the microphone, and each detected Korotkov sound is displayed by a flashing light (LED). The user of the device has to place the cuff on the upper arm, place the microphone over the brachial artery on the upper arm, and inflate and deflate the cuff manually. They also have to read the displayed cuff pressure at the moment the LED starts to flash for systolic and at the moment it ceases to flash for diastolic blood pressure. There are still some of these devices available on the market (see Figure 2). The main applications for these devices are blood pressure measurements in subjects with an irregular heart beat, as oscillometric sphygmomanometers cannot give reliable readings in these situations.



Figure 2 Example of an auscultatory sphygmomanometer, which indicates Korotkov sounds by a flashing LED (red LED on the left). The cuff with the microphone is not shown³.

[Source: [http://www.boso.de/Produktdetails.21.0.html?&tx_produkte_pi1\[showUid\]=34](http://www.boso.de/Produktdetails.21.0.html?&tx_produkte_pi1[showUid]=34)]

Another area of application of automated auscultatory sphygmomanometer is non-invasive blood pressure measurement during ergometric stress testing, because the oscillometric technique cannot be used here due to its sensitivity on arm movement. These devices are fully automated, i.e. they pressurise the cuff automatically and display numerical values of the blood pressure.



Figure 3 Ergometer with automated auscultatory sphygmomanometer³.
[Source: http://testserver.vollewanne.de/de/sana-bike_250f/sana-bike_250f.php]

³ Disclaimer: The devices shown on figures 2 and 3 are only for illustration as examples of the various existing applications irrespective of their validation status. The European Commission does not endorse their use or their manufacturers.)

The reliability of the blood pressure measurement of the automated auscultatory sphygmomanometer described above is highly dependent on the correct placement of the microphone over the brachial artery. Too much noise is another limitation of the application of such devices.

In recent years automated devices have been developed which measure the blood pressure using both the oscillometric and the auscultatory technique. These devices usually place the microphone not in the cuff but in the housing of the device. The Korotkov sound is transferred through the bladder and the hose to the microphone. Some devices give priority to the results determined by the oscillometric method, using the auscultatory signal for identifying artefacts due to arm movement or beats on the cuff. Other devices give priority to results determined by the auscultatory method and use the oscillometric measurement as a backup.

3.6.2. Non-auscultatory mercury-free sphygmomanometers

The non-auscultatory mercury-free sphygmomanometers use the oscillometric technique to measure the blood pressure based on changes in the artery pulsation during cuff inflation/deflation. These alternatives to the mercury sphygmomanometer are easy and uncomplicated to use. They do not use the auscultation technique, and it is easier to train users. Increasingly, they are used by patients for home blood pressure monitoring and also almost exclusively for 24-hour ambulatory blood pressure monitoring. They need very little maintenance, costs vary according to the additional capabilities of the machine, and calibration testing is needed regularly as per the manufacturer's instructions, usually within two years. The inflation of the cuff may be performed manually (semi-automated) or automatically; however, the deflation is controlled by the device.

3.7. Clinical aspects of the alternatives to Hg sphygmomanometers

A wide variety of devices can be used to measure blood pressure and apart from the intensive care setting, the majority remain non-invasive and include non-automated auscultatory devices (aneroid, non-mercury auscultatory), semi-automated and automated devices (that can be used either at the upper arm, wrist or finger). The alternatives to Hg sphygmomanometers have hugely different levels of reliability.

3.7.1. Auscultatory devices

ANEROID devices – These devices are mercury free, commonly used in clinical practice, and require auscultation to determine blood pressure. They consist of a system of bellows and gears that expand to display pressure using a gauge needle and a pressure display. These devices are easily susceptible to damage and drift of the cuff pressure measurement (Waugh et al. 2002) particularly if they are portable (Bailey et al. 1991) and this leads to inaccurate measurements. A recent study in a primary care setting (in the United Kingdom) has shown that more than 50 percent of aneroid devices had a cuff pressure measurement error >3mmHg compared to only 8 percent of mercury and automated devices combined (Coleman et al. 2005). This is consistent with previous literature. It is therefore recommended that these devices undergo a metrological check at least annually, although the implementation of this recommendation appears unlikely especially in primary care (Rouse and Marshall 2001). The number of erroneous readings obtained with aneroid devices is likely to be significant. Improvements in the technology to prevent measurement error may lead to a suitable and accurate alternative to the mercury sphygmomanometer. The use of harmonized ISO/CEN standards will promote further improvement of these devices.

ELECTRONIC non-mercury auscultatory devices: As an auscultatory alternative, electronic devices use a pressure sensor and a digital display (numerical, circular/linear

bar graph). Models such as the Accoson Greenlight 300 (Graves et al. 2004), PMS Mandhaus (Wilton et al. 2006) and Nissei DM-3000 (British Hypertension Society, 2006) have been introduced, all of which have received clinical recommendation following an independent accuracy assessment. As the pressure transducers used within these systems are less prone to measurement error than the bellows in aneroid devices, these auscultatory devices can be assumed to be more reliable if used by a trained observer.

The cuff pressure is displayed as a simulated mercury column using an array of LCDs, and also as a digital LCD readout. The cuff is deflated in the normal way and, when the first and fifth Korotkov sounds indicating systolic and diastolic pressure are heard, a button next to the deflation knob is pressed, which freezes the digital display to show systolic and diastolic pressures, thus offering the potential of eliminating terminal digit preference, which is a major problem with the clinical use of any auscultatory monitor. With such devices, the physician is still able to measure blood pressure using the traditional auscultatory technique, without having necessarily to rely on automated readings, and this is achieved without the problems associated with mercury columns or aneroid devices.

These devices are suitable for patients where clinical conditions such as arrhythmia and pre-eclampsia may preclude the use of automated oscillometric devices. However the reading of such devices cannot be assumed to be equivalent to the reading of a mercury column, where the interpretation of a falling column of mercury with its own inherent dynamics, with an intermittent signal of Korotkov sounds, may not be the same as an electronic alternative. For this reason formal validation is required for any new device being introduced on the market. In addition features that are added to assist with the blood pressure determination, e.g. a hold button, may introduce an error as it does not control for the recognition, and reaction time and may result in a device not reaching an acceptable standard (Stergiou et al. 2008a). However, studies on the physician's reaction time and decision time during blood pressure measurements with this method are in progress to improve the reliability of this approach.

Some non-mercury professional devices allow for both automated electronic (oscillometric) as well as auscultatory blood pressure measurement by an observer using a digital manometer (El Assaad et al. 2002, Omboni et al. 2007, Stergiou et al. 2008b, Stergiou et al. 2008c).

3.7.2. Automated non-auscultatory (oscillometric) devices

There is an ever-increasing market for oscillometric blood pressure devices that have also increased home surveillance such as self-measurement and ambulatory/24hr monitoring. Home blood pressure measurement has been shown to be more reproducible than office blood pressure measurement (Stergiou et al. 2002) more predictive of cardiovascular events (Bobrie et al. 2004, Ohkubo et al. 2004) and reliable when used by non-clinicians (Nordmann et al. 1999). The out-of-office measurements are effective at removing the white-coat effect (Parati et al. 2003) particularly when using an averaging mode (Wilton et al. 2007). Telemonitoring enables the patient to transmit home measurements directly to the clinician's computer for further analysis, potentially enhancing early identification, reducing hospital visits (Pare et al. 2007) and improving the degree of blood pressure control also in general practice (Parati et al. 2009a).

Automated devices are generally intended for use on the upper arm, but finger and wrist devices are also available. Few of these latter devices have been shown to be accurate according to independent accuracy assessments; only a small minority of wrist devices assessed achieved an acceptable accuracy (five in total) (O'Brien and Atkins 2007). Wrist devices are sensitive to errors related to positioning of the wrist at heart level, and some devices have position sensors. Very few of the wrist devices have passed clinical validation after independent assessment (Altunkan et al. 2006, Nolly et al. 2004). However, even the validated wrist devices with position sensors appear to give

significantly different blood pressure values than arm devices in a large proportion of hypertensive patients (Stergiou et al. 2008d), while in an earlier study no such differences were observed (Cuckson et al. 2004). The European Society of Hypertension Guidelines state the preference of arm over wrist oscillometric devices (O'Brien et al. 2003, Parati et al. 2008b). No finger device has yet achieved the established validation standards (Elvan-Taspinar et al. 2003, Schutte et al. 2004).

The oscillometric technique is usually used by automated devices to determine blood pressure by analysing the pressures transmitted through arterial oscillations/vibrations that occur during cuff inflation and/or deflation. The point of maximum oscillation equates to the mean arterial pressure. The recording of pressure waves is dependent on the anatomical position, elasticity and size of the artery, as well as the distribution of the surrounding tissue which is particularly difficult in the wrist. A device specific algorithm equates these signals to the pressure obtained by the pressure transducer. The technique is not generic in any way, and each device must have its algorithm validated.

Automated blood pressure measurement will eliminate the observer errors associated with the use of the manual auscultatory technique such as terminal digit preference, threshold avoidance, observer prejudice, rapid deflation etc. (Beevers et al. 2001). However, clinically significant differences exist between measurements obtained through automation compared to auscultation in many devices. Automated device accuracy is not only device dependent, but also user dependent. As these devices are more likely to be used by untrained individuals, errors related to selecting correct cuff size and taking the recommended arm position, ensuring no movement or talking during device measurement, or allowing for sufficient rest before measurements may be more pronounced than mercury sphygmomanometers. Various guidelines have been published for the correct use of automated devices with specific methodologies advocated (Chobanian et al. 2003, O'Brien et al. 2003, Parati et al. 2008a), but are not as established as training for auscultatory blood pressure measurement.

Automated devices have accuracy limitations in special groups such as those with vascular damage that influences the oscillometric signal: these include patients with diabetes, arrhythmias or pre-eclampsia, and the elderly. This is related to arterial/vascular changes in these patients, which are likely to influence the recording of pressure waves by the device. The British Hypertension Society and some websites list devices that have achieved clinical recommendation under these conditions. Arrhythmias maybe detected by devices fitted with an 'irregular pulse detection' indicator; however, clinical validation for measuring blood pressure during arrhythmias has not yet been performed. This is confounded by not having a reliable reference value as the "gold standard" as mercury sphygmomanometer is itself an indirect measure of blood pressure and how blood pressure relates to this measure is unknown in arrhythmias. A limited number of devices have been validated and found accurate for use in pregnancy (Shennan and de Greeff 2007, Chung et al. 2009) and most of these are inaccurate in pre-eclampsia. There is one anecdotal report of a maternal death in pre-eclampsia when an oscillometric device (not validated for this condition) was used and underestimated the blood pressure level ([Lewis and Drife 2001](#)).

There are some "preliminary positive" data regarding the accuracy of oscillometric devices in "difficult" populations, such as in patients with end-stage renal disease (Thompson et al. 2007), atrial fibrillation (Watson and Lip 2006), the elderly (Omboni et al. 2007) and children (Stergiou et al. 2006). However, it should be realised that there are always some patients in which the oscillometric blood pressure measurement might differ significantly from that taken by a mercury sphygmomanometer without apparent reason, probably influenced by arterial wall properties and pulse pressure (Stergiou et al. 2009, Van Popele et al. 2000,).

An accurate automated sphygmomanometer capable of providing printouts of systolic, diastolic and mean blood pressure, together with heart rate and the time and date of measurement, should eliminate errors of interpretation and abolish observer bias and terminal digit preference. Moreover, the need for elaborate training of observers would

no longer be necessary, although a period of instruction and assessment of proficiency in using the automated device will always be necessary. Another advantage of automated measurement is the ability of such devices to store data for later analysis (Parati G et al. 2008b). This development is in fact taking place, and a number of long-term outcome studies are using automated technology to measure blood pressure instead of the traditional mercury 'gold standard'. For example, in the large Anglo-Scandinavian Cardiac Outcome Trial, the validated Omron HEM-705CP automated monitor was used including thousands of patients followed for about five years (Dahlöf et al. 2005, Hansson et al. 1998, Yusuf et al. 2008).

3.7.3. Conclusions/Discussion

The mercury sphygmomanometer is disappearing from use and there are many alternative devices available to replace it. Blood pressure measurement with the auscultatory technique by a trained observer, using the mercury sphygmomanometer remains the most accurate and reliable form of indirect blood pressure measurement and is currently regarded as the gold standard.

The alternative devices using auscultation have similar limitations as the mercury sphygmomanometers regarding the observer bias associated with auscultation itself. Even though oscillometric instruments are not considered as true "alternatives" to Hg sphygmomanometers because they operate under a completely different principle, those instruments are currently replacing the Hg sphygmomanometers. The advent of accurate oscillometric devices, however welcome, is not without problems. First, oscillometric devices have been notorious for their inaccuracy in the past, although more accurate devices are now appearing on the market. Secondly, most of the available oscillometric devices were designed for self-measurement of blood pressure by patients, and it should not be assumed that they will be suitable for clinical use, or that they will remain accurate with use, although some are being used successfully in hospital practice. Thirdly, oscillometric techniques cannot measure blood pressure accurately in all situations, particularly in patients with pre-eclampsia, arrhythmias such as atrial fibrillation, and there are also individuals in whom these devices cannot measure blood pressure, for reasons that are not always apparent (Stergiou et al. 2009a, Van Popele et al. 2000).

All alternative blood pressure measurement devices need to be clinically validated in clinical protocols against the current gold standard of the mercury sphygmomanometer, until an alternative device is developed and recognised as such. Several international protocols, such as the ISO protocol (in preparation), the British Hypertension Society (BHS) and the European Society of Hypertension (ESH) International Protocol are available for such a clinical validation. A list of validated oscillometric devices is available on dedicated websites, such as the British Hypertension Society as well as other national learned societies.

3.8. Quality requirements for the alternatives to the Hg manometers

3.8.1. General (ISO standards)

In December 2007 the standard ISO 81060-1 "Non-invasive sphygmomanometers – Part 1: Requirements and test methods for non-automated measurement type" was published. This standard addresses all kinds of sphygmomanometers, "which, by means of inflatable cuffs, are used for the non-invasive blood pressure measurement by operator observation" (ISO 2007). Automated sphygmomanometers are addressed in a different standard issued in 2009: IEC 80601-2-30 "Medical Electrical Equipment – Part 2-30: Particular requirements for the basic safety and essential performance of automated non-invasive sphygmomanometers" (ISO 2009). The standard ISO 81060-2 "Non-invasive sphygmomanometers – Part 2: Clinical validation of the automated

measurement type (ISO in preparation). All three standards are expected to become European harmonized standards in the near future.

The ISO 81060-1 addresses requirements for the alternative non-automated sphygmomanometers. Because these requirements are identical for all possible manometers, they include requirements for accuracy of the cuff pressure measurement and for the resistance to vibration and shock. Some requirements are related to the specific needs of aneroid manometers. The ISO/CEN standards are non-mandatory but may be used as tools for checking the reliability of the alternatives to Hg sphygmomanometers and comply with the essential requirements of the medical device directive (93/42/EEC).

3.8.2. Technical Verification

Regular metrological testing is needed to ensure the accuracy of the blood pressure devices. Periodic maintenance and accuracy testing may be initiated by the manufacturers instructions or by legal measures (Germany, Austria, Czech Republic, and Slovakia). Statistical data on the percentage of failure of such verification exist only from ten and more years ago, at that time the number was between eight and ten percent per year (PTB-Mitteilungen, 1990). There is no indication that this number has dramatically changed.

The key element of the verification is the testing of the accuracy of the static pressure measurement by the manometer of the sphygmomanometer. In pressure steps of not more than 50 mmHg over the whole measuring range the error of the pressure measurement has to be determined. For this test a periodically calibrated reference manometer has to be used, usually a digital manometer utilising a piezo-resistant transducer. Mercury manometers are not appropriate for use as reference manometers because their resolution is not good enough and it is not easy to identify the meniscus of the mercury column in order to read exact values (less than 1.0 mmHg).

3.8.3. Clinical validation

Independent device accuracy assessment within a clinical setting is recommended before introduction and routine clinical use. Various protocols have been published to assess automated devices against a mercury sphygmomanometer during clinical use and these are referred to as clinical validation protocols. The International Protocol of the European Society of Hypertension (O'Brien et al. 2002) and the protocol of the British Hypertension Society (O'Brien et al. 1993) are widely accepted, and most commonly used in publications (see Figure 4), although similar protocols exist in Germany and USA SP10 (AAMI 2007). In addition, CEN standards including clinical validation protocols are available for the manufacturers to use (EN 1060-1, 2 and 3, CEN 1995a, 1995b, 1997). In the recent years there has been a steady increase in the clinical validation of blood pressure measurement devices (see Figure 4). All clinical validation protocols require the use of Hg sphygmomanometers as reference but the CEN standards also allow the use of alternative measurement devices.

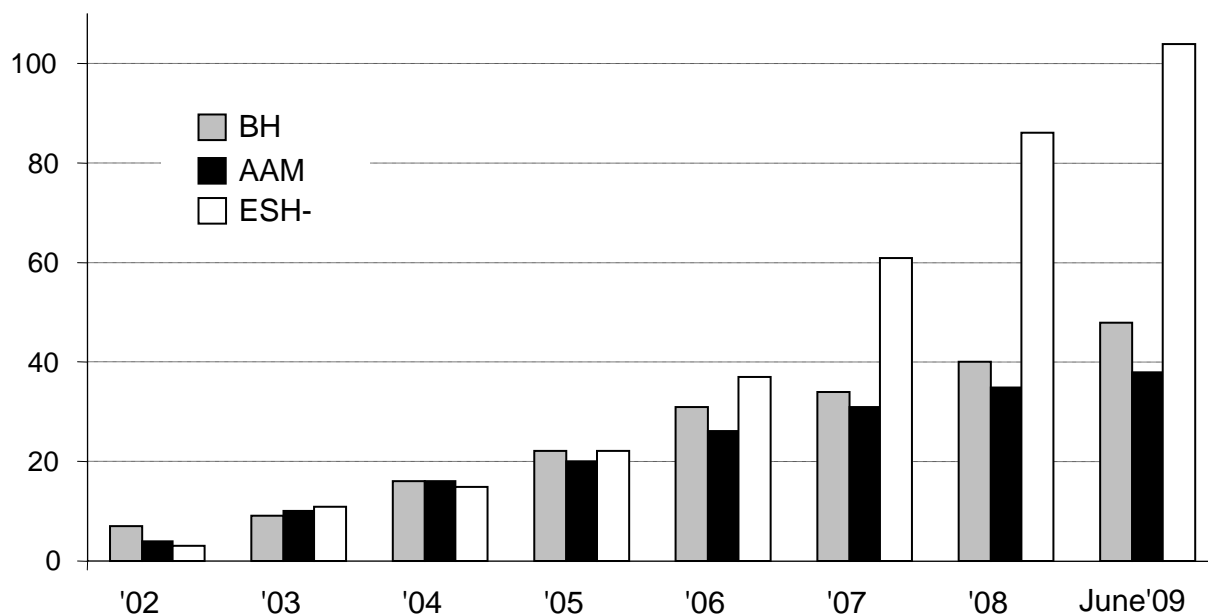


Figure 4 Cumulative graph of validation studies performed according to the European Society of Hypertension International Protocol (ESH-IP) compared to the British Society of Hypertension (BHS) and the US Association for the Advancement of Medical Instrumentation (AAMI) protocols from 2002 until June 2009 (Modified from Stergiou et al. 2009b).

The clinical validation protocols presented on Figure 4 require a series of consecutive blood pressure measurements taken over a wide range of blood pressures using the test device in comparison to the mercury sphygmomanometer as a reference. The accuracy of the test device is graded (A-D – where A or B is a pass) or given a pass/fail for systolic and diastolic pressure accuracy according to each protocol. This is usually based on the number/percentage of differences between observer and device in three categories: differences ≤ 5 mmHg, ≤ 10 mmHg and ≤ 15 mmHg. In addition the mean difference and standard deviation (SD) of the difference is calculated and measured against the ANSI/AAMI SP10-1992 standard (AAMI 2007), which requires a mean difference (SD) ≤ 5 (8) mmHg for clinical recommendation. Devices that have been assessed according to these standards are subsequently listed on the British Hypertension Society and other websites after independent review by the respective committee members of these organisations who give a final verdict as to whether the device should be recommended for clinical use or not, based on whether the protocol guidelines were adequately followed.

Despite the concern that the majority of devices have not yet been validated, it is encouraging to note that the number of validation studies has steadily risen from only 10 in 1990 to 104 studies in 2009 [Stergiou et al 2009b]. The British Hypertension Society and other websites are valuable resources for both clinicians and patients.

3.9. Discussion

Mercury is toxic, and there exists the Community Strategy Concerning Mercury with the aim of restricting the use of mercury. Mercury sphygmomanometers have been instrumental in developing the present knowledge on hypertension as a risk factor for cardiovascular diseases and its control by treatment. Therefore, they are considered the gold standard for blood pressure measurement. The need for accurate clinical measurement will always be present, and the fact that important clinical decisions will

continue to be made on very small numbers of readings (often one, and rarely more than three) emphasizes the need for maximum accuracy.

Several aneroid and automated alternative blood pressure devices have been validated against the mercury sphygmomanometer. Currently there are no reports published on any electronic device that has been validated using aneroid machines. It can be envisioned that in the future one of the alternative blood measurement devices might also be suitable as a reference for clinical validation of newly developed devices. Until a suitable mercury-free device is developed and recognised as a reference for blood pressure measurement, mercury sphygmomanometers will be needed for clinical validation studies of aneroid and automated blood pressure measurement devices.

3.10. Recommendations

It is recommended that for clinical validation studies mercury sphygmomanometers should remain available as reference for alternative mercury-free blood pressure measurement devices.

4. OPINION

Mercury and its compounds are highly toxic to humans, ecosystems and wildlife. Mercury can exist in several chemical forms (Hg^0 , Hg^{1+} , Hg^{2+}), each with its own toxicological profile. In general terms, the toxicity of these chemical forms is highest for the organic mercury compounds, followed by elemental mercury and inorganic mercury compounds. In measuring devices like sphygmomanometers and previously thermometers, elemental liquid mercury is used. A Community Strategy Concerning Mercury was adopted in January 2005 with the key aim of reducing mercury levels in the environment and reducing human exposure. This Opinion addresses the issue of whether the replacement of mercury-containing blood-pressure measuring devices (sphygmomanometers) would (i) endanger proper health care including specific groups of patients, and/or (ii) compromise long term translational epidemiological studies for public health. In addition, the availability and quality of alternative devices for blood pressure measurements have been considered.

Blood pressure measurement is vital for the prevention and treatment of blood pressure related diseases, and for monitoring cardiovascular homeostasis. The indirect measurement of blood pressure with mercury sphygmomanometers (applying the auscultatory technique) has identified arterial hypertension as a major risk factor for cardiovascular diseases. The auscultation method is based on the observation of the recurrence of the blood flow in the occluded artery (using a cuff) of the upper arm by listening to the sounds generated by the recurrent blood flow and disappearance of the sounds when the occlusion is completely removed (by dilation of the cuff), and normal blood flow is restored. In addition to use in clinical settings the mercury sphygmomanometer is also used in long-term epidemiological/observational studies on cardiovascular disease development. A change in population blood pressure has a direct effect on the morbidity and mortality of cardiovascular diseases. Based on long-term experience, blood pressure measurement using the mercury sphygmomanometer is regarded as the gold standard method for indirect measurement of blood pressure. Several factors, however, affect the measurement of blood pressure including the technical skills of the observer, the inherent variability of blood pressure, the accuracy of the device, and the difficulty in measuring blood pressure in some special groups (e.g. the elderly, patients with arrhythmias, patients with a large arm, children, and pregnant women). The use of the mercury sphygmomanometer has practical and technical limitations, and requires specific training. In addition, there should be a special emphasis on regular maintenance of the mercury sphygmomanometer in order to maintain its accuracy. When blood pressure is measured by a trained observer using the auscultatory technique, the mercury sphygmomanometer currently remains the most accurate device for indirect blood pressure measurement.

The mercury column functions as a pressure sensing and displaying component, so it seems likely that this can be replaced by a mercury-free manometer. Indeed, mercury-free alternatives for pressure measurement are commercially available such as the aneroid manometer and the electronic pressure transducer. These alternative sphygmomanometers use auscultation for determination of the blood pressure, and therefore, have the advantages and limitations (such as the observer performance) which also apply to the mercury sphygmomanometer, and are characteristic of the auscultatory technique. In addition, there are non-auscultatory, non-mercury devices available which use the oscillometric technique to measure blood pressure based on changes in arterial pulsation during cuff inflation/deflation. Oscillometric instruments operate under a completely different principle and are thus not considered as true "alternatives" to Hg sphygmomanometers. The various alternatives have widely varying levels of accuracy, emphasising the importance of clinical validation. Regular maintenance is of the utmost importance for proper functioning of all measurement instruments. Even validated oscillometric devices may have accuracy limitations in special patient groups, including patients with arrhythmias, diabetes, the elderly and pre-eclampsia. This is related to the arterial/vascular changes in these patients affecting the oscillometric signal. These

limitations do not apply to devices using the auscultatory technique. Therefore, validated non-mercury auscultatory alternatives are appropriate for these patients.

For alternative blood pressure measurement devices a metrological verification is needed to ensure the accuracy of the measurements. In addition, an independent device accuracy assessment is recommended to evaluate the clinical performance. Various clinical validation protocols are available to assess the accuracy of automated alternative devices against mercury sphygmomanometers.

In conclusion, the mercury sphygmomanometer is gradually disappearing from clinical use and there are several appropriate alternatives available. When blood pressure is measured by a trained observer using the auscultatory technique, the mercury sphygmomanometer or a validated auscultatory alternative currently remains the most accurate instrument for indirect blood pressure measurement, especially for certain patient groups. The alternative devices using auscultation have similar limitations as the mercury sphygmomanometers regarding the observer technique and bias associated with auscultation itself. These may be avoided by using automated oscillometric devices, which, when properly validated, allow accurate blood pressure measurements. For all blood-pressure measuring devices, regular maintenance is of primary importance.

In order to maintain a high-level quality of blood pressure measurements it is recommended that mercury sphygmomanometers remain available as reference standards for clinical validation studies of existing and future non-mercury-containing blood-pressure measurement devices. It is emphasised that mercury devices should remain available as standards until an alternative standard is developed and recognised.

4.1. Specific answers to questions raised in the Terms of Reference

Question 1

Is there sufficient evidence to demonstrate that mercury-free blood pressure measuring devices such as aneroid or electronic instruments are *generally reliable* substitutes for mercury-containing sphygmomanometers?

Yes. There is sufficient scientific evidence that mercury-free blood pressure measuring devices (when clinically validated) are generally reliable substitutes for mercury-containing sphygmomanometers in routine clinical practice. These alternative devices include both auscultatory devices requiring a trained observer, and also automated oscillometric devices for which some instruction is needed.

Question 2

Have mercury-free sphygmomanometers been adequately validated over a *wide range* of blood pressures, ages, and clinical conditions to allow for routine use in hospitals and outpatient settings?

Yes. Clinically validated, auscultatory mercury-free devices are equivalent to mercury sphygmomanometers. For the oscillometric devices the situation is different as these devices have mainly been clinically validated in adult populations including a wide range of blood pressures but not in a wide range of ages and clinical conditions.

Question 3

Have mercury-free sphygmomanometers been adequately validated for the diagnosis of hypertension in *specific clinical conditions* such as arrhythmia, pre-eclampsia in obstetrics and certain vascular diseases?

Yes. Clinically validated, auscultatory mercury-free devices are equivalent to mercury sphygmomanometers, and are thus suitable for these specific groups of patients. In addition, some oscillometric devices have achieved accuracy in certain conditions although in others, like arrhythmias, the auscultation technique is necessary. Moreover,

there is a need for more clinical validations of oscillometric devices to make them usable in specific groups of patients, including elderly patients, children, and pre-eclamptic women.

Question 4

Are mercury-based sphygmomanometers essential as reference devices for *validation* of long-term clinical epidemiological studies enrolling patients with hypertension?

Yes. Mercury-containing sphygmomanometers are considered essential as reference devices for the clinical validation of the alternatives. For on-going, long-term epidemiological studies currently using mercury sphygmomanometers it is advisable not to change the method of measurement. Therefore, it will be necessary to keep mercury sphygmomanometers available in order to compare them with the alternatives in these studies.

Question 5

Are mercury-based sphygmomanometers essential as reference devices for *calibration* of the mercury-free sphygmomanometers when the latter are used for routine diagnostic purposes?

No, they are not essential as reference devices for the metrological verification (calibration) needed to ensure the accuracy of the measurement of the blood pressure devices. In general, more accurate manometers are available for metrological verification.

Question 6

Is SCENIHR aware of any *adverse effects* for patients' health due to the replacement of mercury-containing sphygmomanometers by mercury-free alternatives?

No evidence was found for adverse effects for patients' health in clinical settings due to the replacement of mercury-containing sphygmomanometers by validated mercury-free alternatives. There are adequate alternatives in most clinical condition/setting. In special conditions, such as pre-eclampsia, non-mercury auscultatory devices should be preferred until further validation of oscillometric devices.

5. MINORITY OPINION

None

6. LIST OF ABBREVIATIONS

AAMI	Association for the Advancement of Medical Instrumentation
ABPM	Ambulatory Blood Pressure Measurements
ANSI	American National standard Institute
BHS	British Hypertension Society
CEN	European Organisation for Standardisation
EEC	European Economic Community
ESH	European Society of Hypertension
ESH-IP	European Society of Hypertension International Protocol
Hg	Mercury
IEC	International Electrotechnical Commission
ISO	International Organisation for Standardisation
LCD	Liquid Crystal Display
LED	Light-Emitting Diode
OIML	Organisation Internationale de Métrologie Légale (International Organization of Legal Metrology)
PTB	Physikalisch-Technische Bundesanstalt
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SI	Système international d'unités (International System of Units)

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