TempleGuard use cases described by literature study

Literature study and parameters analysis

Atherosclerotic Arteriopathy (AA) is a degenerative process starting as soon as the late childhood and characterized by increasing thickness and stiffness of the arteries. AA is favorized by various noxious factors including diabetes, smoking or dyslipidemia and is the main cause of cardiovascular morbidity and mortality worldwide. Nevertheless, AA is considered as a “silent killer” being mostly asymptomatic before the development of severe and/or irreversible complications. One of the most frequent clinical manifestations of AA is essential arterial hypertension affecting up to 30% of the general population. [1] Arterial blood pressure is directly related to ischemic heart diseases and stroke. [2] An increase of blood pressure of 20/10 mmHg increases the cardiovascular risk by roughly 50%. Coronary artery disease and ischemic heart disease, other manifestations of AA, are the leading cause of death worldwide. [3]

Therefore, early detection and close monitoring of the development of AA is of utmost clinical importance.

Unfortunately, currently the screening for AA is limited to the assessment of cardiovascular risk factors and office blood pressure (BP) measurements. The last one relaying on readings taken by a physician using a mercury sphygmomanometer cuff, an outdated method implemented more than 100 years ago or more recent oscillometers. Moreover, office BP measurements is subject to known limitations. In particular, the prevalence of false positives results (white coat effect) are estimated to be as high as 20 % in the hypertensive population. [4] Even more difficult to detect, false negatives results (masked hypertension) are almost as common (15%). [5] Self-monitoring oscillometers for home BP monitoring (HBPM) have been implemented to overcome these limitations and better assess the effect of treatment. However, the measurement are usually performed twice a day at rest giving limited information and they can induce useless stress or compulsive use in some patient.

To overcome these limitations 24h ambulatory blood pressure (24h-ABPM) monitoring is increasingly used with better predictive results. [6] 24h-ABPM with its regular measurement (every 15 to 30 min) allows a better coverage of the BP profile throughout one day and one night, absence of nocturnal BP dipping having shown to be an important predictor of coronary artery stenosis, left ventricular hypertrophy or lower cognitive performance. [7] Even worst, inverse dipping is associated with poor cardiovascular prognosis for both cardiac events and stroke. [8] Nonetheless, 24h-ABPM provides many BP, but only over a one day period, providing a measure of only short-term variability. Frequent Cuff inflation is too uncomfortable in particular at night for longer measurement, and 24h-ABPM is often inaccurate during physical activities, limiting the number of variables available for such analysis. Shultz et al. demonstrated that systolic BP measured during light to moderate exercise predicts the presence of masked hypertension with high specificity in individuals with a hypertensive response to exercise. [9] Kim et al. investigated hypertension in marathon runners and found that exercise induced hypertension was associated with increased

prevalence of coronary artery plaques and could be a new risk factor for coronary artery plaque formation. [10]

Taken all together, these limitations have resulted in numerous research to develop new cuffless devices capable of continuous monitor of the blood pressure over serial days. [11] Previous approaches have focused on watch like device based on pulse wave analysis (PWA). [12] Despite considerable efforts, results have been disappointing so far. Indeed, due to their location near the wrist at the end of the upper extremity signal is often parasitized by movement artefacts and the devices are difficult to calibrate by the patient.

TempleGuard is an easy wearable device attached to existing eyeglasses, continuously measuring patient's vital signs behind the ear including arterial blood pressure. As the head has only central movement of low amplitude the signal is extremely accurate. Furthermore, compared to the extremities, right and left side head movement and blood perfusion are symmetrical, allowing simultaneous measurement of the right and left occipital arteries.

Since arterial hypertension occurs relatively late in the development of AA, we have also looked for another earlier biomarker of AA. In multiple scientific study, Pulse wave velocity (PWV, a measure of arterial stiffness) has been shown to predict cardiovascular outcomes even before the development of hypertension.[13] Using mechanotransducers directly applied on carotid and femoral artery, the speed of propagation of the pulse is recorded and distance between these arteries is measured in order to determine the PWV. It's utility increases in importance both for routine clinical assessment of patients and for clinical studies. Arterial stiffness increase with age and the presence of cardiovascular risk factors such as hypertension. Gender differences doesn't influence PWV. [14] Normal and reference values for PWV according to the age category are resumed on the table 1. [14]

Table 1: Normal values of PWV (m/s) according to the age category

Age (years)	Mean (±2 SD)
<30	6.2 (4.7-7.6)
30-39	6.5 (3.8-9.2)
40-49	7.2 (4.6-9.8)
50-59	8.3 (4.5-12.1)
60-69	10.3 (5.5-15.0)
≥70	10.9 (5.5-16.3)

PWV: pulse wave velocity; SD: standard deviation

Increased PWV is a risk factor for hypertension and stroke. [15] Pathophysiological conditions associated with increased arterial stiffness are shown on the table 2. [15]

Table 2. Clinical conditions associated with increased arterial atiffness

Ageing	Other physiological conditions
CV risk factors	Low birth weight
Obesity	Preeclampsia
Hypertension	In vitro fertilization
Diabetes	Genetic backround
Dyslipidemia	Lack of physical activity
Smoking	Non-CV diseases
CV diseases	Chronic kidney disease
Coronary heart disease	Rheumatoid arthritis
Congestive heart failure	Systemic vasculitis
Stroke	Systemic lupus erythematosus

CV: cardio-vascular

clinical implementation of PWV is not possible on a routine basis. TempleGuard offer a unique opportunity to overcome this issue.

TempleGuard prototype-device is able to collect good quality ECG signal, allowing measurement of heart rate, calculation of heart rate variability (HRV), [16] and detection of cardiac arrhythmia including atrial fibrillation.
HRV refers to the fluctuation in the time intervals between adjacent heartbeats. [17] Low HRV is a long-recognized predictor of cardiovascular mortality or sudden cardiac death. [18] [19] [20] [21] [22] [23] More recently, dedicated algorithms have been developed to predict the risk of coronary artery disease (CAD) based on the analysis of HRV.[24] [25] In particular, the multicenter HRV-DETECT (Heart Rate Variability for the Detection of Myocardial Ischemia) trial has shown that low HRV was independently associated with a significant 2-fold increased likelihood for myocardial ischemia [26] in a cohort of 1043 patients at low or intermediate risk for CAD.
Atrial fibrillation (AF) is both a cause and a result of cardiovascular diseases. AF is a supraventricular tachyarrhythmia caused by uncoordinated atrial electrical activation and consequently ineffective atrial contraction characterized by an irregularly irregular pulse. [27] The presence of AF is a strong risk factor of adverse cardiovascular outcomes or death, [28] particularly in women.[29] Especially, the presence of AF increases 5 times the risk of stroke,[30] and up to 2 times the risk of death.[28] Recently the apple heart study has highlighted the potential value of smartwatch (Apple Watch, Apple Inc, Cupertino, CA) to detect AF by measuring irregular pulse using an integrated photoplethysmography sensor [31] but at the price of high false positive rate. Therefore, new generations of Apple Watch have been developed with built-in ECG electrodes capable of performing a single-lead ECG. However, active participation of the watch carrier is still needed. Indeed, it is only after the positioning of the index finger of the opposite hand on the watch crown, which creates a closed circuit from the wrist wearing the Apple Watch and the user's fingertip of the opposite hand, that an ECG signal can be acquired. Compared to the first lead of a 12-lead ECG the signal gained

by the Apple watch is of respectable accuracy.[32] ECG characteristics of AF are irregularly irregular R-R intervals, absence of distinct repeating P waves, and irregular atrial activations.[27] Algorithms have been developed to automatically detected the presence of AF. In an Apple Watch manufacturer validation study a dedicated algorithm (ECG app 2.0) was able to detect AF with a specificity of 99.3 %, and the sensitivity of 98.5 % compared with ECGs recorded with a reference device and interpreted by independent clinical experts.[33] Recent study in a clinical setting found sensitivity of 94.6% and specificity of 100% for the same algorithm.[34]
To conclude, measurement of the electrical cardiac activity by TempleGuard using built-in ECG lead offers the unique possibility to continuously record an ECG signal of good quality without the active participation of the subject. Based on our algorithm, we will be able to use these data to predict cardiovascular risk but also to detect the presence of AF.

Usability study App

The development of an application is ongoing. All the vascular data gained by the TempleGuard will be further combined with the individual risk factors (i.e. family history of cardiovascular diseases, smoking), and morphometric parameters (age, BMI). All these information will be integrated using artificial intelligence and data processing, we aim to estimate the overall cardiovascular risk long before cardiovascular events occur. Finally, a smart devices (smart-phone) will send appropriate indication to the subject for further steps that would be needed (i.e. consultation with a family doctor). We will use already established scores (i.e. Score2) [35, 36] for the validation of our application.

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