ORIGINAL ARTICLE

Nocturnal Hypertension and Cardiovascular Events at a Buenos Aires City Hospital

Hipertensión nocturna y eventos cardiovasculares en un hospital de la ciudad de Buenos Aires

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ABSTRACT

Background: Nocturnal Hypertension (NHT) has an impact on cardiovascular morbidity and mortality. Our aim was to evaluate the association between NHT and cardiovascular events.
Methods: We carried out a retrospective cohort study including adults which had an ambulatory blood pressure monitoring test between March 2017 and July 2020 at a hospital in Buenos Aires City Argentina, with up to 36 months follow-up. Univariate and multivariate analyzes were performed to identify associated factors.
Results: Four hundred and ninety four patients were included in the final analysis, 48% male, average age 58.9 years. Sixty two percent (n=308) presented NHT. A higher incidence of the cardiovascular composite endpoint was found in this group compared to those who did not present it, 10.4% vs 3.8% (p=0.013). In the final multivariate Cox regression analysis NHT was an independent predictor of cardiovascular events (HR= 3.9; 95% CI 1.56–9.81; p= 0.001), even independently of daytime HTN and the different circadian patterns of pressure.
Conclusions: In this contemporary cohort from Buenos Aires, NHT was related to cardiovascular events incidence. Different measures should be taken to increase NHT awareness and diagnosis.

Key Words: Hypertension - Cardiovascular Disease - Blood Pressure Monitoring, Ambulatory

RESUMEN

Introducción: Nuestro objetivo fue determinar si la hipertensión arterial nocturna (HTAN) se asocia a eventos cardiovasculares o mortalidad en el seguimiento.
Material y métodos: Estudio de cohorte retrospectiva que incluyó pacientes adultos que se realizaron una presurometría ambulatoria en un hospital de la ciudad de Buenos Aires, incorporados a un registro propio entre marzo de 2017 y julio de 2020, con seguimiento de hasta 36 meses de la presurometría índice. Se realizaron análisis uni- y multivariados para identificar factores asociados.
Resultados: De 522 sujetos, se incluyeron 494 en el análisis final. El 48% era de sexo masculino y la edad promedio fue de 58,9 años. El 62% (n=308) presentó HTAN. Se halló una mayor incidencia del punto final compuesto cardiovascular en este grupo en comparación con quienes no la presentaban, 10,45 VS 3,8% (p=0,013). El análisis final por regresión de Cox multivariada demostró que la HTAN fue un predictor independiente de eventos cardiovasculares (HR= 3,9; IC 95% 1,56–9,81; p= 0,001), incluso independientemente de la HTA diurna y de los diferentes patrones circadianos de presión.
Conclusión: En una cohorte contemporánea y de la ciudad de Buenos Aires, el patrón de HTAN se asoció con la aparición de desenlaces cardiovasculares. En base a estos hallazgos, se deben implementar medidas para incrementar su diagnóstico en nuestro medio.

Palabras clave: Hipertensión arterial - Enfermedad cardiovascular - Monitoreo ambulatorio de la presión arterial

INTRODUCTION

Arterial hypertension (HTN) is a risk factor with significant impact on cardiovascular (CV) morbidity and mortality. According to the World Health Organization (WHO), in 2008, approximately 40% of adults aged 25 and above had been diagnosed with HTN; the prevalence of HTN is highest in the African Region (46%), the lowest is found in the Americas (35%). (1) Subsequently, in order to implement an epidemiological surveillance system of HTN in our country, the Argentine Society of Cardiology and the Argentine Federation of Cardiology jointly designed the 2nd National Registry of Hypertension (RENATA-2 Study), concluding that the prevalence of hypertension in Argentina is 36.3%,

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consistent with WHO reports. (2)

Blood pressure (BP) is affected by demographic factors, such as age, race, and sex; intrinsic factors, such as neurohormonal regulation (sympathetic nervous system and renin–angiotensin–aldosterone system) and extrinsic factors, such as sleep quality, lifestyle, smoking and alcohol intake. (3) Early diagnosis, prevention, and optimal management of HTN are essential; its increased prevalence is associated with population aging and behavior, unhealthy diet, alcohol abuse, physical inactivity, overweight, and stress, among other factors. (4)

BP follows a pattern of circadian rhythm, with values 10-20% lower during sleep than during waking hours. Over the past decade, there has been an explosion of knowledge about nocturnal hypertension (NHT) and alterations in circadian patterns. Nocturnal BP is the minimum BP required for organ perfusion during rest, and individuals with higher nocturnal BP have a negative impact on the cardiovascular risk. (3) Diabetes mellitus, chronic kidney disease and obstructive sleep apnea are the three diseases most frequently associated with NHT.

Some people experience a moderate nocturnal decrease in BP (< 10% of daytime pressure), a phenomenon known as non-dipper pattern; other people have a significant nocturnal increase in BP called reverse dipper; the extreme dipper pattern, in which nocturnal BP falls by more than 20%, is less common. Those patterns have been associated with increased target-organ damage and adverse cardiovascular (CV) events. (4) Whether NHT per se or altered circadian patterns are responsible for CV events still remains unclear.

Therefore, our purpose was to determine whether NHT is associated with follow-up mortality or CV events.

METHODS

Study design

We carried out a retrospective cohort study, including patients who underwent 24-hour ambulatory blood pressure monitoring (ABPM) for NHT diagnosis, or for prognostic purposes in hypertensive subjects, at a hospital in Buenos Aires, Argentina, from March 2017 to July 2020.

The primary endpoint was the composite of major adverse cardiovascular events, MACE (nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) , death from other causes, hospitalization or visit to the emergency service due to heart failure (defined by Framingham criteria), hospitalization for an episode of HTN urgency/emergency, and acute coronary syndrome (ACS).

Each of those events separately were considered secondary endpoints.

Study population and definitions

We created our own database including patients > 18 years who underwent ABPM in the Department of Cardiology of a hospital in Buenos Aires City.

Registry variables included: a) identification data, sex, age, weight, body mass index (DuBois formula), pathological history and classic cardiovascular risk factors; b) ABPM: date of test, percentage of successful readings, 24-h average, daytime and nighttime average, pulse pressure, nocturnal pattern of blood pressure behavior (dipper, non-dipper, reversed dipper, or extreme dipper); c) lab testing: creatinine and creatinine clearance (Cockroft-Gault formula) prior to the study and at follow-up; d) echocardiography: atrial size, septal and posterior wall thickness, left ventricular ejection fraction (LVEF) (Simpson's method); and e) antihypertensive therapy, specifying the drugs; and statins and aspirin use.

Patients with technically unsatisfactory studies, duplicate ABPM reports (the first record was included), and patients whose follow-up data could not be obtained were excluded. Follow-up was conducted through the electronic medical records in the institution; maximum follow-up time was 36 months after index ABPM.

In accordance with the American Heart Association (AHA) criteria, nocturnal hypertension was defined based on a BP value ≥ 120/70 mmHg during the passive/nighttime period, and daytime hypertension as a BP value ≥ 135/85 mmHg, both referred to by the follow-up sheet. (7)

Procedures

MEDITECH® ABPM 05 blood pressure monitors were used, with oscillometric method and an accuracy of ± 3 mmHg/ 2% of the measured value according to the manufacturer's technical specifications. Monitors were programmed to take measurements every 15 minutes during the active period and every 60 minutes during the passive period across 24-hour intervals. Data collection analysis and reporting software was provided by the manufacturer.

Follow-up was conducted by a group of 4 of the study researchers through the electronic medical records in the institution, and in cases of incomplete or missing data, contact and follow-up were performed by phone calls and closed questions for up to 36 months from the index ABPM.

Statistical analysis

Statistical analyses were performed with R Studio, version 1.4.1106 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation or median and interquartile range, depending on their type of distribution. Qualitative variables were expressed in absolute and relative frequencies, Qualitative variables were compared using the chi-square test or Fisher's exact test, while continuous variables with parametric and nonparametric distribution were compared using Student's T-test and the Mann Whitney U-test, respectively. Multiple imputation of the database was performed for the treatment of missing data using the random forest method, since most of the variables to be imputed were categorical. (8) Univariate and multivariate analyses were performed to identify factors associated with cardiovascular events. A Cox regression model was used to search for predictors of events in long-term follow-up. For the univariate analysis, patients were divided into 3 age ranges (45 to 66 years, 67 to 80 years, and 81 to 98 years); in addition, the original variable for circadian blood pressure patterns was grouped into 2 categories based on the presence or absence of nocturnal blood pressure drop (dipper vs non-dipper). All variables with p value < 0.20 in the bivariate analysis or considered clinically relevant were included in the multivariate model. Nested models were chosen according to the Akaike information criterion (AIC). Kaplan Meier curves and log-rank tests were performed for the variables associated to follow-up events. Incidence and predictors of events were expressed as hazard ratios with their CI 95%. All tests were two-tailed, and statistical significance was set at $p < 0.05$.

Ethical considerations

Researchers adhere to the National Data Protection Act (No 25326), the Declaration of Helsinki, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS). To avoid bias, four of the authors had access to the personal data of the cases analyzed, and masked the information, which was sent to the researchers with no personal data to perform the statistical analysis and the final review. As this was a retrospective study, participants signed the usual institutional informed consent form by which the information from institutional medical records may be used for observational scientific research.

This article was developed following the STROBE guidelines.

RESULTS

Baseline characteristics of the population

Out of 522 patients at baseline, 18 did not meet the definition of arterial hypertension, 8 had incomplete ABPM data, and 2 patients had no follow-up; therefore, 494 subjects were included in the study population (Figure 1). Of them, 48% were male, mean age 58.9 ± 14.6 years. Baseline characteristics are summarized in Table 1.

Three hundred and eight subjects (62%) had NHT. Compared with non-NHT patients, NHT group had increased body mass index (BMI), higher frequency of diabetes mellitus, and greater wall thickness on echocardiography. Mean daytime and nighttime blood pressure and pulse pressures were significantly higher in the NHT group. Regarding antihypertensive treatment, there were no significant differences in the use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARA II), beta-blockers and diuretics, whereas a significantly higher use of calcium channel blockers was found in the NHT group compared to the non-NHT population (Table 1).

Events per groups

The primary endpoint was present in 39 patients during a median follow-up of 835 (455-1091) days, 32 (10.4%) in the NHT group and 7 (3.8%) in the non-NHT group ($p = 0.013$). There were 17 HTN-related consultations to the emergency service: 14 from the NHT group and 3 from the non-NHT group ($p = 0.13$); no significant differences in the incidence of MACE were found, 12 in NHT (3.9%) and 3 in non-NHT (1.6%) patients ($p = 0.24$); there were 5 deaths due to cardiovascular events, all of them in the NHT group. Primary endpoint event-free survival is shown in Figure 2. Combined-event survival was lower in the NHT group versus the non-NHT group (log-rank test $p = 0.0043$). The NHT group presented increased incidence of urgency/emergency hospitalizations for HT episodes (Figure 3, supplementary material).

In the univariate analysis, age, ventricular hypertrophy, day/night pulse pressure, and left atrial enlargement were not statistically significant and were excluded from the final adjusted model. Daytime NHT, though not statistically significant, was included as a variable of interest, given the importance of adjusting NHT effect by this variable. Univariate analysis HRs for the primary endpoint of our study are detailed in Table 2.

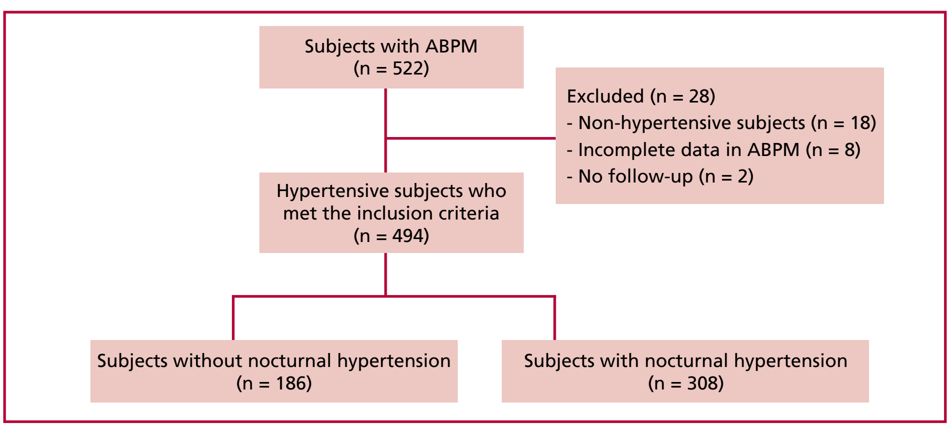
In the final adjusted Cox regression model (Table 3), smoking (HR 3.23, 95% CI 1.62 - 6.40; $p < 0.001$) and NHT (HR 3.9, 95% CI 1.56 - 9.81; $p = 0.001$) were independent predictors of CV events at long-term follow-up (Figure 4, supplementary material). NHT, even when adjusted by daytime HT, remained an independent event predictor. Furthermore, the non-dipper pattern, associated with an increased risk of combined events in the univariate analysis, was ruled out as independent variable in the multivariate analysis.

DISCUSSION

We conducted a retrospective analysis of HTN patients who had undergone ABPM. We found that NHT was independently associated with an increase in the combined number of cardiovascular events at follow-up, with hospitalization for episodes of HT emergency/emergency, and with a tendency to be associated with MACE and cardiovascular death.

HTN is the main modifiable cardiovascular risk

Fig. 1. Flowchart



ABPM: ambulatory blood pressure monitoring

Table 1. Baseline characteristics of the population

Characteristics		Total (494)	Nocturnal HT - No (n=186)	Nocturnal HT - Yes (n=308)	*P* value
Male subjects (n, %)		240 (48.5)	89 (47.8)	151 (49.0)	0.872
Age (mean,SD)		58.95 (14.65)	59.45 (14.44)	58.69 (14.80)	0.576
BMI (median [IQR])		28 (25.0032.00)	27.00 (24.22 – 30.00)	29.00 (26.00 – 33.27)	< 0.001
Dyslipidemia (n, %)		168 (34.3)	61 (33.0)	107 (34.9)	0.743
Sedentary lifestyle (n, %)		206 (41.8)	69 (37.3)	137 (44.6)	0.133
Diabetes (n, %)		75 (15.2)	16 (8.6)	59 (19.2)	0.002
Smoking (n, %)		122 (24.8)	54 (29.2)	68 (22.2)	0.105
Acute coronary syndrome (n, %)		21 (4.3)	5 (2.7)	16 (5.2)	0.270
Stroke (n, %)		22 (4.5)	11 (5.9)	11 (3.6)	0.316
Atrial fibrillation (n, %)		12 (3.2)	2 (1.3)	10 (3.8)	0.226
LVEF (median [IQR])		68.00 (64.00 – 70.00)	68.00 (64.00 – 70.00)	68.00 (64.00 – 70.00)	0.985
IVS (mean SD)		11.21 (1.72)	10.77 (1.63)	11.48 (1.72)	< 0.001
PW (median [IQR])		10.00 (9.00 – 11.00)	10.00 (9.00 – 11.00)	11.00 (9.70 – 12.00)	< 0.001
CrCl (median [IQR])		92.88 (66.80 – 116.82)	87.98 (66.87 – 109.01)	95.48 (66.78 – 121.11)	0.331
ACEI (n, %)		148 (29.9)	50 (26.9)	98 (31.8)	0.290
ARA II (n, %)		168 (33.9)	57 (30.6)	110 (35.7)	0.291
Calcium blockers (n, %)		121 (24.4)	32 (17.2)	89 (28.9)	0.005
Thiazides (n, %)		59 (11.9)	20 (10.8)	39 (12.7)	0.623
Anti-aldosterone agents (n, %)		11 (2.2)	6 (3.2)	5 (1.6)	0.393
Beta-blockers (n, %)		125 (25.3)	49 (26.3)	76 (24.7)	0.759
Statins (n, %)		147 (29.7)	56 (30.1)	90 (29.2)	0.914
Aspirin (n, %)		78 (15.8)	30 (16.1)	48 (15.6)	0.985
Daytime SBP (median [IQR])		135.00 (126.50 – 145.00)	126.00 (118.00 – 133.00)	141.00 (133.00 – 151.25)	< 0.001
Daytime DBP (median [IQR])		79.00 (71.00 – 86.00)	74.00 (68.00 – 80.00)	83.00 (75.00 – 90.00)	< 0.001
Day pulse pressure (median [IQR])		56.00 (48.00 – 65.00)	51.00 (45.00 – 58.00)	59.00 (51.00 – 69.00)	< 0.001
Night pulse pressure (median [IQR])		54.72 (46.00 – 63.00)	47.42 (8.57)	59.31 (13.02)	< 0.001
Pattern (n,%)	Dipper	283 (57)	118 (63.4)	165 (53.6)	
	Attenuated dipper	69 (14)	16 (8.6)	53 (17.2)	
	Reversed dipper	25 (5.1)	0 (0.0)	25 (8.1)	
	Extreme dipper	59 (11.9)	45 (24.2)	14 (4.5)	
	Non-dipper	58 (11.7)	7 (3.8)	51 (16.6)	

SD: standard deviation; IQR: interquartile range; BMI: body mass index; LVEF: left ventricular ejection fraction; IVS: interventricular septum; PW: posterior wall; CrCl: creatinine clearance; ACEI: angiotensin-converting enzyme inhibitors; ARA II: angiotensin II receptor antagonists; SBP: systolic blood pressure; DBP: diastolic blood pressure.

factor, and it is possible that NHT phenotype —with a higher degree of dysautonomia— presents a higher risk. In order to quantify the absolute impact of NHT, as a measure of absolute risk, the attributable risk and attributable fraction percentage were calculated, which were 6.63 (95% CI 2.26 - 11) and 63% (95% CI, 19.69 - 83.68), respectively. This means that NHT was directly and independently responsible for 63% of the events in our cohort of patients.

Ours is a relatively young patient population, with mean age close to 60 years; 62% of patients had NHT. They had a higher rate of comorbidities than the non-NHT group (diabetes, overweight and higher degree of ventricular hypertrophy). This is consistent with patient populations from previous studies, in which the main conditions associated with NHT are diabetes, chronic kidney disease, overweight/obesity, older age, obstructive sleep apnea, and sedentary lifestyle. (6)

In their study, Boggia et al (9) determined that daytime blood pressure predicts fatal combined with non-fatal cardiovascular events, regardless of HT treatment status. Moreover, in the Belgian study by Fagard et al (10) on 3468 HT patients without cardiovascular disease, daytime and nighttime systolic and diastolic blood pressure were assessed by ABPM;

Fig. 2. Event-free survival in patients with and without nocturnal hypertension

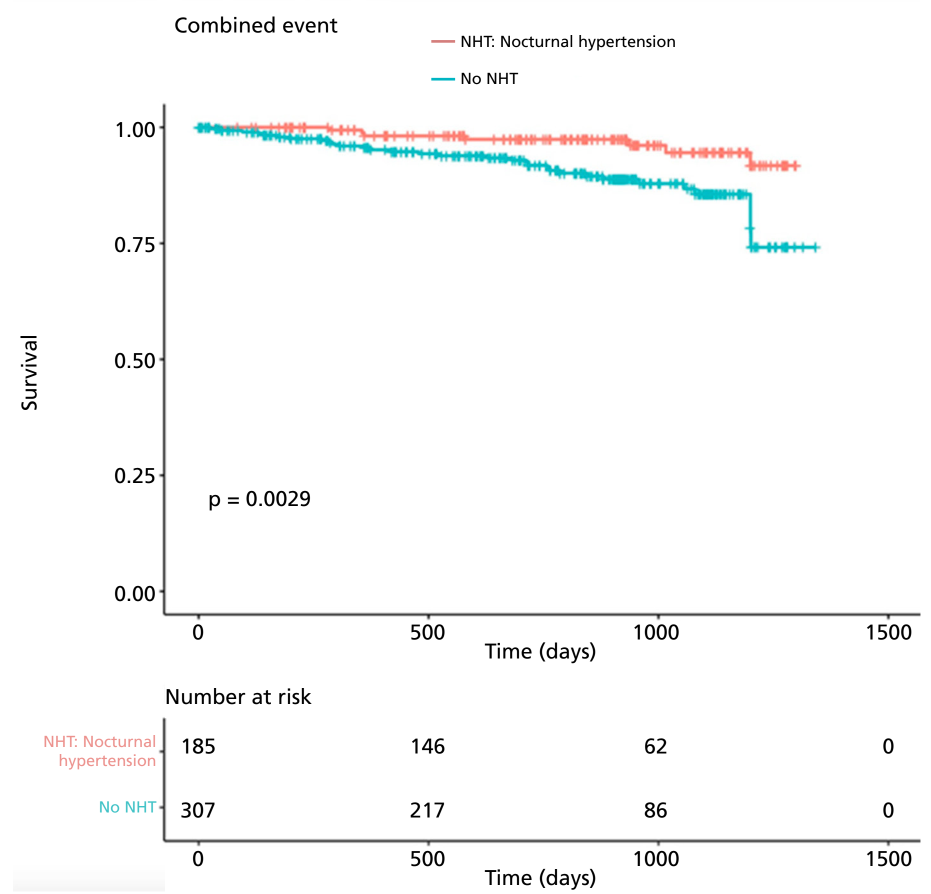


Table 2. Relative risk of combined events associated with the different cardiovascular risk factors, univariate analysis

Factor		HR	*P* value
NHT		3.24	0.004
Smoking		3.19	< 0.001
Diabetes		2.00	0.0516
	(42-66)	1.23	0.738
Age (years)	(67-80)	1.99	0.271
	(81-98)	3.05	0.145
Dyslipidemia		1.79	0.067
Increased night PP		1.49	0.503
Increased day PP		0.84	0.785
Daytime HTN		1.45	0.259
Non-dipper pattern		3.66	0.003
Interventricular septum		1.88	0.250
Left atrial enlargement		1.79	0.162
OSAHS		0.94	0.959
Sedentary lifestyle		19.47	0.041

PP: pulse pressure; NHT: nocturnal hypertension; HTN: Hypertension; OSAHS: obstructive sleep apnea-hypopnea syndrome.

Factor	HR	*P* value
NHT	3.92 (1.56 –9.81)	0.003
Smoking	3.23 (1.62 –6.40)	0.001
Diabetes	1.24 (0.58 –2.62)	0.578
Dyslipidemia	1.33 (0.66 –2.63)	0.426
Sedentary lifestyle	1.16 (5.75 –2.32)	0.682
Daytime HTN	0.81 (0.39 –1.65)	0.567
Non-dipper pattern	1.59 (0.55 –4.61)	0.380

NHT: nocturnal hypertension; HTN: Hypertension

Table 3. Multivariate analysis.

it was found that only nocturnal pressure (especially systolic pressure) predicted cardiovascular events during 7-year follow-up. Neither daytime systolic nor diastolic blood pressure added prognostic accuracy to adjusted models. Our observations provide similar information in a cohort from the City of Buenos Aires, with slight phenotypic differences, contributing to increase NHT validation as a predictor of cardiovascular events, regardless of HTN in general.

Importantly, our results show that despite the fact that the group of patients with nocturnal hypertension also had daytime hypertension, NHT remained a significant and independent predictor of the daytime pressure value in the adjusted Cox model. There is no clear explanation as to why nocturnal pressure is a better predictor, but it could be associated with nocturnal pressure being more stable, so the measurement could be more representative.

NHT is an interesting entity, usually connected with non-dipper and reverse dipper patterns. An important —yet unanswered— question is which of these two entities —NHT or non-dipper status— is more responsible for target organ damage and negative impact on cardiovascular events (11, 12). In our study, this pattern was associated with events only in the univariate analysis and not in the multivariate adjusted model.

Our study has some limitations. Firstly, it was carried out in a single center; however, it included a heterogeneous population with similar characteristics to previous studies. Secondly, the retrospective design entails bias; while we performed a multiple regression analysis to control possible confounders, we cannot completely rule out the presence of variables that may have altered our results. Thirdly, as this is a relatively healthy population in primary prevention, we believe that longer follow-up will determine the impact on total and cardiovascular mortality with more certainty.

In conclusion, in our population, NHT pattern was directly and independently associated with cardiovascular outcomes at 36-month follow-up. Longer follow-up is required to determine whether such a pattern correlates with total mortality.

Conflicts of interest
None declared.
(See authors' conflict of interests forms on the web/Additional material.)

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