Ambulatory electrocardiographic monitoring in stable coronary artery disease and preserved LV function
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Ambulatory electrocardiography can be used to detect arrhythmias, transient myocardial ischemia and to analyze heart rate variability. This thesis describes the latest insights in the use of the last two applications, in patients with documented coronary artery disease. Aims of this thesis were to study transient myocardial ischemia and heart rate variability, their relation as well as the association with other clinical parameters such as coronary angiography. In addition, the effect of lipid-lowering therapy on transient myocardial ischemia was assessed. Most of the studies were part of the Regression Growth Evaluation Statin Study (REGRESS), a double blind, placebo controlled study to assess the effect of two year treatment with pravastatin, on progression and regression of angiographically documented coronary atherosclerosis in male patients with normal to moderately raised serum cholesterol levels (4 and 8 mmol/L).

Reports on the value of transient myocardial ischemia in normal subjects with risk factors are disappointing. In our studies the selection of patients comprised a lesion of at least 50% on coronary angiography. We were therefore convinced that the ST segment depression on the ambulatory electrocardiographic monitoring really reflected ischemia (Chapter 2). The pronounced long and short term variability in ischemia was also discussed in this chapter. For our study on the effect of pravastatin on myocardial ischemia (Chapter 9) the long and short term variability of ischemia is not a major problem, since we compared against a placebo group in which this variability is presumed to be present at an equal level. Moreover, no selection was performed to patients with and without ischemia as all patients and all recordings were analyzed. As discussed, optimal recording time constitutes a 48 hour period as used in our studies. Chapter 3 gives more information on endothelial function with a special attention on hypercholesterolemic endothelial dysfunction. Hypercholesterolemic and atherosclerotic coronary endothelial dysfunction consist of a progressive, not irreversible, impairment in reactions to various endothelium dependent relaxing substances in both epicardial coronary artery as in resistance vessel. Paradoxical vasoconstriction, dynamic stenoses and dysregulation of the coronary blood flow make this endothelial dysfunction contribute to the pathogenesis of myocardial ischemia. The selectivity of the impairment makes the concept of specific receptor opening on doses of oxidized free fatty acids levels of oxidized low density lipoprotein receptors, the mechanism of EDRI. In chapter 4, the 885 patients with normal coronary angiogram. The percent diffuse atherosclerosis in group B versus 0.06 mm difference between treatment group and placebo group at the end of the therapy with pravastatin patients. The patients were asymptomatic no matter whether they had or not moderately raised serum cholesterol levels than in the placebo group did not differ significantly in baseline characteristics. In chapter 5 to 8, analysis of heart rate and arrhythmias. In 51 consecutive patients with coronary artery disease, sex, beta adrenergic receptor, 24 hour ambulatoryholter monitoring and heart rate variability.
SUMMARY AND CONCLUSIONS

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Receptor operated signal transductions in hypercholesterolemia and low doses of oxidized LDL likely. In progressive atherosclerosis and high levels of oxidized LDL the dysfunction may spread onto other receptors, the availability of L-arginine may decrease and the metabolism of EDRF changed. As has been reported recently, cholesterol-lowering therapy restores this endothelial dysfunction.

In chapter 4 the main results of the REGRESS study are reported. Of the 885 patients included, 778 patients (88%) had an evaluable final angiogram. The mean mean segment diameter (mainly reflecting diffuse atherosclerosis) decreased 0.10 mm in the placebo group versus 0.06 mm in the pravastatin group \( P = 0.019 \): the mean difference between treatment groups was 0.04 mm with a 95% confidence interval (CI) of 0.01 to 0.07 mm. The median minimum obstruction diameter (mainly reflecting focal atherosclerosis) decreased 0.09 mm in the placebo group versus 0.03 mm in the pravastatin group \( P = 0.001 \): the difference of the medians between the treatment groups was 0.06 mm with a CI of 0.02 to 0.08 mm. At the end of the follow-up period 89% (CI 86 to 92%) of the pravastatin patients and 81% (CI 77 to 85%) of the placebo group patients were without cardiovascular events \( P=0.002 \). In symptomatic men with significant coronary atherosclerosis and normal to moderately elevated serum cholesterol, those who were treated with pravastatin significantly less progression of coronary atherosclerosis and fewer new cardiovascular events were observed than in the placebo group. The beneficial effect of pravastatin did not differ significantly between the four quartiles with regard to baseline cholesterol levels.

Chapter 5 to 7 discuss the use of ambulatory monitoring for the analysis of heart rate variability (HRV) in relation to ischemia and arrhythmias. In chapter 5 we studied if autonomic regulatory mechanisms and circadian variation play a role in transient myocardial ischemia in patients treated with beta adrenergic blockade. In 51 consecutive patients with angiographically documented coronary artery disease, stable angina and transient myocardial ischemia, despite beta adrenergic blockade.

24 hour ambulatory electrocardiographic monitoring for ST depression and heart rate variability analysis was performed. Despite therapy,
258 episodes of transient ischemia were recorded. At heart rates at onset of ischemia < 70 beats per minute a high ratio of low- to high frequency power accompanied the ischemic events, paralleled by a remarkable reduced high frequency power. The high ratio, i.e. enhanced sympathetic tone during ischemia, was mainly found in the early morning. By contrast, ischemic episodes with onset heart rates ≥ 70 beats per minute were not associated with significant changes in the parameters of autonomic function. We concluded that during beta-blockade, the residual transient ischemia was associated with decreased heart rate variability. The ischemia-related change in the autonomic nervous system during the early morning hours was in agreement with previous studies, showing increased cardiovascular risk at this time of the day.

As the autonomic nervous system and ischemia are related, is there a specific group at risk, showing both depressed HRV and ischemia? And what is the role of non-sustained ventricular arrhythmias, do they reflect high risk patients? In chapter 6 we studied the correlations of heart rate variability and transient myocardial ischemia with other clinical parameters using ambulatory electrocardiographic recordings from 312 patients with significant coronary artery disease and a left ventricular ejection fraction of ≥ 30%. Only those patients, who had both episodes of ischemia and non-sustained ventricular arrhythmias showed diminished values for parasympathetic non-spectral and spectral HRV parameters. The root mean square of difference of successive RR intervals (RMSSD) and high frequency power (HF) in this group were 28 ± 3 ms and 9 ± 1 ms respectively. The highest values of these HR variability parameters were found in patients with non-sustained ventricular tachycardia and no ischemia (81 ± 21 ms and 14 ± 1 ms, respectively, p ≤ 0.05). A relation was seen between transient myocardial ischemia and low frequency power as well as between transient ischemia and ventricular tachycardia. These data suggested that the autonomic nervous system may play a role in ischemia as well as in ischemia related ventricular arrhythmias. In selected groups of patients the relation of depressed heart rate variability is highly predictive for adverse outcome. Of note, most of the patients investigated also had a reduced left ventricular ejection fraction or a history of arrhythmias. In the REGRESS trial only patients with a left ventricular ejection fraction > 30% were included. In a subgroup this trial we studied the correlation of depressed HRV with all clinical events. Low heart variability was found in 280 consecutive patients with unstable angina pectoris 71 ± 12%. Clinically significant ischemia was associated with decreased heart rate variability. Low measures of heart rate variability were found in patients with no ischemia, this relation appeared to have clinical significance. In patients with ischemia, heart rate variability and left ventricular function were predictors of adverse clinical events. From previous studies and angiographical data, one may conclude that transient myocardial ischemia was associated with increased cardiovascular risk.

As the autonomic nervous system and ischemia are related, is there a specific group at risk, showing both depressed HRV and ischemia? And what is the role of non-sustained ventricular arrhythmias, do they reflect high risk patients? In chapter 6 we studied the correlations of heart rate variability and transient myocardial ischemia with other clinical parameters using ambulatory electrocardiographic recordings from 312 patients with significant coronary artery disease and a left ventricular ejection fraction of ≥ 30%. Only those patients, who had both episodes of ischemia and non-sustained ventricular arrhythmias showed diminished values for parasympathetic non-spectral and spectral HRV parameters. The root mean square of difference of successive RR intervals (RMSSD) and high frequency power (HF) in this group were 28 ± 3 ms and 9 ± 1 ms respectively. The highest values of these HR variability parameters were found in patients with non-sustained ventricular tachycardia and no ischemia (81 ± 21 ms and 14 ± 1 ms, respectively, p ≤ 0.05). A relation was seen between transient myocardial ischemia and low frequency power as well as between transient ischemia and ventricular tachycardia. These data suggested that the autonomic nervous system may play a role in ischemia as well as in ischemia related ventricular arrhythmias. In selected groups of patients the relation of depressed heart rate variability is highly predictive for adverse outcome. Of note, most of the patients investigated also had a reduced left ventricular ejection fraction or a history of arrhythmias. In the REGRESS trial only patients with a left ventricular ejection fraction > 30% were included. In a subgroup this trial we studied the correlation of depressed HRV with...
heart rates at the set heart rates were paralleled by a spectral ratio, i.e. 
I found in the patients who had had an event, compared to patients with no event. Adjusted for differences in baseline characteristics, this relation remained statistically significant. Healthy volunteers appeared to have the highest measures.

In patients with ischemic heart disease and normal or near normal left ventricular function decreased heart rate variability is associated with adverse clinical events.

From previous studies only little information was available of the angiographical base of transient myocardial ischemia. Some critics state that transient myocardial ischemia reflect only little myocardium at jeopardy and therefore should not be treated as such.

In chapter 8 the relation of transient myocardial ischemia with coronary angiography was discussed. In 203 of 771 men transient myocardial ischemia was observed. At baseline, transient myocardial ischemia was associated with a statistically significant higher incidence of three vessel coronary artery disease, irregular lesions and calcified segments (P = 0.001, 0.002 and 0.007, respectively). Progression of coronary artery disease was more extensive in the transient myocardial ischemia group, both by visual and quantitative analysis (ischemia versus non-ischemia group: progression of 3.3 (10.7) percent diameter stenosis versus 1.5 (5.8) percent, P = 0.007, progression in mean segment diameter 0.09 (0.18) versus 0.08 (0.20) mm, P = 0.20, change in minimum obstruction diameter 0.15 (0.43) versus 0.09 mm, P = 0.027, respectively). Duration of ischemia was correlated to future clinical events, time to first event and progression of disease. Time from randomization to unscheduled percutaneous transluminal coronary angioplasty (PTCA) and to unscheduled coronary artery bypass graft operation (CABG) was shorter in patients with transient myocardial ischemia (135 (80) versus 221 (189) days, P = 0.049 and 144 (64) versus 239 (122), P = 0.008 respectively). We concluded that transient myocardial
ischemia on the ambulatory electrocardiogram identifies patients with extensive coronary artery disease, prone to instability and progression of coronary lesions. Further study is needed whether this type of ischemia can be used for risk stratification of patients on the waiting list for CABG or PTCA.

As we know from these data that transient myocardial ischemia reflects patients with more active and possibly more vasoactive lesions, it is of importance to speculate on whether this type of ischemia is related to endothelial dysfunction.

Based on the knowledge about endothelial function and hypercholesterolemia (chapter 3), we continued to study the 2 years effect of pravastatin 40 mg on transient myocardial ischemia as detected by a 48 hour ambulatory electrocardiogram (chapter 9). In the patients randomized to pravastatin transient myocardial ischemia was present at baseline in 28 percent and after treatment in 19 percent, in the placebo group this was in 20 percent and in 23 percent of the patients, respectively (P = 0.021 for change in percentage between two treatment groups, odds ratio (OR) 0.62, 95 percent confidence interval (CI) 0.41 to 0.93). Ischemic episodes decreased by 1.23 (SE 0.25) episode with pravastatin and by 0.53 (SE 0.25) episode with placebo (P = 0.047). Under pravastatin the duration of ischemia decreased from 80 minutes (SE 12) to 42 minutes (SE 10, P = 0.017), and with placebo from 60 minutes (SE 13) to 51 minutes (SE 9, P = 0.56). The total ischemic burden decreased from 41 millimeter.minute (SE 5) to 22 millimeter.minute (SE 5) in the pravastatin group (P = 0.0058) and from 34 millimeter.minute (SE 6) to 26 millimeter.minute (SE 4) in the placebo group (P = 0.24).

Adjusted for independent risk factors for the occurrence of ischemia, the effect of pravastatin on the reduction of risk for ischemia remained statistically significant (OR 0.45, 95 percent CI 0.22 to 0.91, P = 0.026).

We concluded that in men with documented coronary artery disease and optimal anti-anginal therapy pravastatin reduces transient myocardial ischemia. Although further study is needed, the implications of these findings might include prescription of lipid-lowering therapy to all patients with angina pectoris, not only to lower their total and cardiac mortality but also to reduce ischemia and to prevent PTCA or CABG. In line with this we discussed in chapter 10.

**Summary and Conclusions**

In this thesis we found a 40 mg for 2 years to conventional therapy. We found a reduction in unscheduled CABG or PTCA related to all cause mortality and more than three vascular deaths as well. In patients with better endothelial function, transient ischemia on the ambulatory electrocardiogram was a correlation with the occurrence of myocardial ischemia in patients with a history of coronary artery disease. The appearance of transient myocardial ischemia pattern paralleled to the results of Survival Study and the follow-up on patients treated with simvastatin or placebo. Relative risk reduction was significantly lower in the simvastatin group. Incremental benefit was seen for the cholesterol level at the upper quartile (4.0-5.0 mmol/l) during simvastatin treatment. Patients aged 60 to 70 years had a lower event rate. Since we found a 50 percent risk reduction, we suggested that simvastatin was effective in reducing the risk of cardiovascular events. We also concluded that in men with documented coronary artery disease and optimal anti-anginal therapy, pravastatin reduces transient myocardial ischemia. Although further study is needed, the implications of these findings might include prescription of lipid-lowering therapy to all patients with angina pectoris, not only to lower their total and cardiac mortality but also to reduce ischemia and to prevent PTCA or CABG.
SUMMARY AND CONCLUSIONS

In this thesis we demonstrated that the administration of pravastatin 40 mg for 2 years reduced transient myocardial ischemia additional to conventional therapy including CABG and PTCA. In line with this we found a relation with ischemia to a shorter time to first unscheduled CABG and PTCA; ischemia of a long duration was related to all clinical events. Patients with this type of ischemia have more three vessel disease and more progression of coronary artery disease as well as a higher incidence of irregular and calcified lesions. In patients with stable coronary artery disease and preserved LV function, transient myocardial ischemia on the ambulatory electrocardiogram reflects the extent of disease and its activity and has a correlation with adverse outcome.

The appearance of transient myocardial ischemia follows a circadian pattern paralleled by changes in heart rate variability. An autonomic
influence on this type of ischemia is suggested, resulting in an impaired coronary vasomotion.
Ambulatory electrocardiographic monitoring in stable angina pectoris patients, documented coronary artery disease and preserved left ventricular function offers the possibility for an objective and quantitative study for ischemia and triggers for ischemia. Exercise testing will detect only ischemia at higher heart rates. Although more expensive than an exercise test, ambulatory monitoring can be applied to observe whether anti-ischemic treatment is optimal and to predict coronary instability. A more liberal use of ambulatory electrocardiographic monitoring might be of help in this low risk population, especially when also heart rate variability is used.

Future research might be directed towards the clinical value of transient myocardial ischemia in patients waiting for PTCA and CABG. Abolishment of all ischemia probably will remain the main purpose of future study, either by revascularisation, lipid lowering, ACE inhibition or other new anti-ischemic modalities.

Dutch Summary/Nederlandse Samenvatting

Een 24 uurs of 48 uurs draagbaar electrocardiogram (Holter) wordt in de cardiologie toegepast om ritmestoornissen ischemie (zuurstofgebrek) van de hartspier op te sporen. Recent is het mogelijk gebleken om een Holter ook te gebruiken voor de analyse van hartslagvariabiliteit.
Het doel van dit proefschrift was om met name het effect van ischemie en hartslagvariabiliteit alsmede hun onderlinge relatie te bestuderen. Hiernaast werden de prognostische kenmerken van beide onderzocht en werd hun verhouding met andere klinische parameters bekeken. Vooral ging de aandacht uit naar het effect van cholesterol verlagende medicatie (pravastatine/Selektine®) op het voorkomen van ischemie gedurende de studie.
De meeste Holter studies waren een onderdeel van “REGRESS” (Regression Growth Evaluation Statin Study), een multi-centrum studie onder auspiciën van het Interuniversitair Cardiologisch Instituut Nederland (ICIN), met als doel het effect van 2 jaar behandeling met pravastatine te bestuderen op pro- en regressie van significant coronarylijder een cholesterol hart (linker k Tijdelijke ischemie in de waanhebbende hartspier. Bij verhoogd zijn van de beken van zuurstof te de functie van van ischemie. In hoofdstuk 5 bij patiënten waarschijnlijk een bestond uit patiënten hadden, in op ST segment af ischemie ook worden de betal alsmede de variabiliteit van ischemie detectie van ischemie. In hoofdstuk 7 Hypercholesterol specifieke receptor van de concentratie (hiervan) zijn dit worden betrokken. Cholesterol oxidantia herst el veroorzaakte een. In hoofdstuk 4 Van de 885 per tweede angiografie. Pravastatine (S) reduceerde de gemiddelde diabetes. 2 jaar was er een pravastatine groei.
SUMMARY AND CONCLUSIONS

Coronary artery disease. It concerned 885 male patients with angina pectoris, a cholesterol value between 4 and 8 mmol/L and with a good left ventricular function.

Tidal ischemia on the Holter can be caused by a mismatch between oxygen demand and oxygen supply to the myocardium. With an increased heart rate, the demand for oxygen will increase, further narrowing of the blood vessel at the site of the usual obstruction or at another place will result in oxygen deficiency. In this context, there is much interest in the function of the vessel wall (endothelial function).

In chapter 2, it is pointed out that the detection of ischemia in patients who are not known with coronary artery disease may not yield much. The investigated group in this thesis consisted of patients who all had a narrowing of more than 50% and at least one coronary vessel. It is assumed that the ST segment deviations on the Holter electrocardiogram that are consistent with ischemia also represent ischemia. Furthermore, the limitations of the method and technique are discussed, as well as the variability in the measurements. For the analysis of variance, a 24-hour analysis is sufficient, whereas for the detection of ischemia a 48-hour analysis is preferred. In this chapter, the latest guidelines for variation of ischemia are also discussed.

In chapter 3, attention is paid to endothelial function. Hypercholesterolemia causes endothelial dysfunction because a specific receptor on the endothelial cell is blocked. At higher concentrations of LDL cholesterol (and in particular the oxidized form of it) more receptors are involved in this process. Cholesterol-lowering medication, but also diet and antioxidant therapy can restore the endothelial dysfunction caused by hypercholesterolemia.

In chapter 4, the main article of the REGRESS study is printed. Of the 885 patients who took part in this study, 778 could use the second angiogram for comparison with the first. Pravastatine (SelektrineR) 40 mg per day, given for 2 years, reduced the angiographic progression of stenosis (both in average vessel diameter and minimal diameter). After two years, there was a clear reduction in clinical endpoints in the pravastatin group.
Hoofdstuk 5 tot 7 behandelen de mogelijkheid om met Holter hartslag variabiliteit te meten. In een subgroep van patiënten (hoofdstuk 5), waarbij ischemie persisteerde ondanks bèta blokkerende medicatie, werd bestudeerd of hart slag variabiliteit veranderd voor, na en gedurende ischemie. Naast een gevonden circadiaan patroon in ischemie samenhangend met hartslag variabiliteit werd een sterke verandering in hartslag variabiliteit gevonden in die patiënten die ischemie bij een lage hartfrequentie kregen ten opzichte van diegenen met ischemie bij een hoge hartfrequentie. Geconcludeerd werd dat autonome beïnvloeding vooral bij ischemie bij lage hartfrequenties van belang lijkt. In hoofdstuk 6 werd gezocht naar een relatie tussen abnormale hartslagvariabiliteit met ischemie en ritmestoornissen. Het bleek dat patiënten zonder ischemie met korte ventriculaire ritmestoornissen (non-sustained ventricular tachycardia) in de onderzochte groep een hoge hartslagvariabiliteit hadden. Een groep met ernstige ischemie en ventriculaire ritmestoornissen had de slechtste hartslag variabiliteit. Op grond van de resultaten werd geconstateerd dat in een kleine groep patiënten er mogelijk een autonome beïnvloeding is van ritmestoornissen enerzijds en ischemie anderzijds. Welke invloed een lage hartslag variabiliteit heeft op klinische eindpunten werd onderzocht in hoofdstuk 7. Vroegere publicaties lieten een duidelijk voorstellende waarde zien van hartslagvariabiliteit met name bij patiënten met een gestoorde linker ventrikelfunctie. In de REGRESS studie waren alleen patiënten opgenomen met een linker ventrikel ejectie fractie van > 30%. Bij 280 patiënten werd hartslag variabiliteit gemeten. In de groep patiënten met een klinisch eindpunt (sterfte, myocardinfarct, PTCA, CABG en beroerte) was met name de hartslag variabiliteit component SDANN verlaagd. Werden deze waarden vergeleken met gezonde proefpersonen dan hadden de laatstgenoemden de hoogste waarden. In hoofdstuk 8 werd onderzocht in hoeverre de groep van patiënten met ischemie op de 48 uurs Holter qua coronair angiogram en klinische eindpunten verschilde van de groep zonder ischemie. In 203 van de 771 patiënten werd ischemie aangetroffen. Aandoeningen in alle 3 coronairvaten kwam vaker voor in de groep met ischemie, alsmede irregulaire letsels en verkalking van de vaten. Na 2 jaar werd in de groep met ischemie meer progressie van afwijkingen gevonden, gemeten met quantitatieve coronairangiografie en met de visuele panel beoordeling (do tussen ischemie en ischemie omdat een groc geopereerd werd eerder een spoec met een duur eindpunten. In hoofdstuk 3 werd effect op coronair vragen van dit pr oorspronkelijke c holerol verlag gevonden wordt. De ischemie ver begijn van de stude gerandomiseerde patiënten. Aan respectievelijk 19 van ischemie in placebogroep. De pravastatine groe resultaten werd ischemische eigen angineuze sympto minder patiënten ondernomen. In hoofdstuk 10 verbonden zijn aan tezamen met de grond van de 45 coronairlijden ge c reductase remmen van cholesterol ver van het uitgangs gesteld dat bij bijn een statine overw
SUMMARY AND CONCLUSIONS

beoordeling (door 3 onafhankelijke cardiologen). Een directe relatie tussen ischemie en klinische eindpunten werd niet gevonden, mogelijk omdat een groot aantal patiënten al aan het begin van de studie geopereerd werd (CABG). Wel moesten patiënten met ischemie veel eerder een spoed CABG of PTCA ondergaan en was ernstige ischemie met een duur van > 30 minuten wel gerelateerd met klinische eindpunten.

In hoofdstuk 3 werd geconstateerd dat cholesterolverlaging een gunstig effect op coronair endotheeldysfunctie heeft. Een van de belangrijkste vragen van dit proefschrift wordt beantwoord in hoofdstuk 9. Blijkens het oorspronkelijke ontwerp van de REGRESS studie vragen we ons af of cholesterol verlaging effect heeft op ischemie zoals die op de Holter gevonden wordt. Hierbij werd er van uitgegaan dat een gedeelte van de ischemie veroorzaakt wordt door endotheeldysfunctie. Aan het begin van de studie was ischemie in 28% van de naar pravastatine gerandomiseerde patiënten aanwezig en in 20% van de placebo patiënten. Aan het einde van de studie was dit aanwezig in respectievelijk 19 en 23% van de patiënten. Dit betekende een daling van ischemie in de pravastatine groep en een stijging in de placebo groep. De ernst van de ischemie nam het meeste af in de pravastatine groep ten opzichte van placebo. Op grond van deze resultaten werd gesuggereerd dat pravastatine (Selektine®) anti-ischemische eigenschappen heeft. Verder onderzoek moet uitwijzen of angineuze symptomen met dit medicament ook verdwijnen, waardoor minder patiënten in de toekomst een PTCA of CABG te hoeven ondergaan.

In hoofdstuk 10 werd nagegaan wat voor klinische consequenties er verbonden zijn aan de recente onderzoeken met cholesterolverlaging tezamen met de in dit proefschrift gepresenteerde resultaten. Op grond van de 4S, WOS en REGRESS studie zijn er bij patiënten met coronairlijden geen subgroepen aan te geven waarin de HMG CoA reductase remmers niet effectief zijn. Het overtuigende klinisch effect van cholesterol verlagende medicatie was aanwezig ongeacht de hoogte van het uitgangscholesterol. Als conclusie in dit hoofdstuk werd gesteld dat bij bijna iedere angina pectoris patiënt een behandeling met een statine overwogen moet worden.