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Cardiovascular Risk in Inflammatory Bowel Disease: Another Reason to Control Disease Activity

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"Major adverse cardiovascular events" (MACE) are an important endpoint for clinical trials of agents used in chronic inflammatory conditions. The risk of MACE and venous thromboembolism are elevated among patients with inflammatory bowel disease (IBD). Concerns about increased risk of MACE were noted in the ORAL Surveillance trial of tofacitinib versus anti-TNF agents in rheumatoid arthritis, but deeper analyses suggest that most of this risk is borne by a high-risk group older than 65 years who are current/former smokers. In IBD trials, the risk of MACE does not appear to be elevated.

INTRODUCTION

When we refer to the term "MACE," we are not talking about the spice, the anti-personnel spray or the medieval weapon, we are talking about "major adverse cardiovascular events." It is important to understand the definition of MACE used in a particular study. The classic definition of MACE is "3-point MACE", which is non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. Some definitions of MACE include hospitalization for congestive heart failure (CHF), and some include both hospitalization for CHF and hospitalization for unstable angina. Thus, to compare risks across studies, you need to examine the specific definition of MACE used.[1]

PATHOGENESIS OF ATHEROSCLEROSIS IN INFLAMMATORY DISORDERS

We are beginning to understand the role of inflammatory cytokines in atherosclerosis associated with inflammatory conditions. Most inflammatory conditions are throwing off pro-inflammatory cytokines such as interleukin (IL)-36, IL-1-beta (β), IL-6, and tumor necrosis factor-alpha (TNF-α). Some of these will amplify the T-cell adaptive response, and the TH1 effector cells will generate more TNF-α, which is pro-atherogenic, whereas the TH17 effector cells will produce IL-17,

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which, depending on the circumstances, can be either pro-or anti-atherogenic.[2] TNF-α plays a role in a prothrombotic state through various mechanisms, such as platelet aggregation and endothelial cell activation, whereas IL-1 can increase LDL cholesterol oxidation, and contribute to accelerated atherosclerosis and plaque rupture.[3] The proposed mechanism of atherosclerotic cardiovascular disease in inflammatory bowel disease (IBD) is multifactorial, including genetic predisposition, environmental risk factors which contribute to a compromised gut microbiome, including bacterial overgrowth and disruption of the intestinal barrier, and then immune dysregulation, resulting in systemic inflammation including TNF-α, C-reactive protein (CRP), IL-1, and vascular epithelial growth factor. This leads to endothelial cell dysfunction with production of lipopolysaccharide, oxidase of damage, and macrophage activation. This, along with certain medications, as well as atherosclerotic cardiovascular disease (ASCVD) risk factors such as tobacco use, diabetes mellitus, poor diet, and obesity, lead to accelerated atherosclerosis.[4]

CARDIOVASCULAR RISK: SCOPE OF THE PROBLEM

A meta-analysis of five studies, with over 2400 cerebrovascular events, found that the relative risk of cerebrovascular disease was elevated in patients with IBD.[5] The pooled risk for any IBD was 1.18 (95% CI, 1.09-1.27). For Crohn's disease, the pooled risk was 1.26 (95% CI, 1.14-1.39), and for UC it was 1.13 (95% CI, 1.05-1.23). The relative risk was higher amongst women (1.28) than men (1.11). The relative risk was higher among patients younger than 40 or 50 years of age, with a relative risk of 1.84, than among older patients, with a relative risk of 1.11. The same meta-analysis examined the risk of ischemic heart disease in patients with IBD and included six studies with over 6400 cardiovascular events in over 123,000 IBD patients.[5] For any IBD, the relative risk was 1.18 (95% CI, 1.07-1.31). For CD, the relative risk was 1.10 (95% CI, 1.03-1.17), and for UC it was 1.14 (95% CI, 1.03-1.25).

A population-based study of Olmsted County, Minnesota residents diagnosed with IBD between 1970 and 2011 assessed the risk of myocardial infarction in 736 IBD patients along with two matched controls per case.[6] Despite lower rates of traditional ASCVD risk factors in the IBD patients, including family history of coronary artery disease, cigarette smoking, and hyperlipidemia, the cumulative risk of acute myocardial infarction was significantly higher among IBD patients compared to matched controls (P<0.001, log-rank tests). Overall, the adjusted hazard ratio for myocardial infarction was 2.82 (95% CI, 1.98-4.04). The hazard ratio was higher amongst users of corticosteroids relative to their matched controls, which indirectly suggests that inflammation may be one of the mechanisms of action behind the association. Similarly, the risk of heart failure was significantly higher among IBD patients compared to their matched controls (P<0.02).[6] The adjusted hazard ratio for heart failure was 2.03 (95% CI, 1.36-3.03). Again, the hazard ratio was higher amongst steroid users relative to their matched controls, suggesting that inflammation may be playing a role.

In a prospective study of 361 unselected IBD patients who underwent coronary artery calcium scoring, 41% had a score of 0, 29% had a score between 1 and 99, 17% score between 103 and 199, and 13% scored greater than 400.[7] Over half of the patients had an estimated 10-year ASCVD risk estimated greater than 7.5%. Patients with higher calcium scores were more likely to start a statin and more likely to start aspirin. The survival free of MACE was significantly higher among patients with a calcium score less than 76 relative to those greater than 76 (P<0.001, log-rank test).[7] A calcium score greater than 76 was associated with a 4-fold increased risk of MACE.

A retrospective study of premature cardiovascular disease among U.S. military veterans was performed.[8] Patients with extremely premature cardiovascular disease, defined as occurring under the age of 40 years, were significantly more likely to have IBD than their matched controls without cardiovascular disease (odds ratio [OR], 1.61; 95% CI, 1.34-1.94).

The United Kingdom Biobank is a large population-based prospective study of over half a million participants aged 40-69 years, with detailed data on cardiac risk factors, and outcomes from primary care visits, hospitalizations, and death

registry.[9] Patients in this biobank with IBD were matched to four non-IBD controls on the basis of age, sex, body mass index, ethnic background, smoking and alcohol usage, hypertension, diabetes mellitus, and hyperlipidemia. The primary outcome of this analysis was a composite of myocardial infarction, cerebrovascular accident, and cardiovascular death. Median follow-up was 12.4 years. The survival free of this endpoint was significantly higher in the non-IBD patients (P=0.011, log-rank test). Overall, patients with IBD had a 19% higher risk of acute arterial events relative to the non IBD patients (adjusted hazard ratio, 1.19; 95% CI, 1.08-1.32).[9] When examining subtypes of acute arterial events, there was a significant association between IBD and ischemic heart disease. There were trends for myocardial infarction and peripheral arterial disease. For premature acute arterial events, IBD was independently associated with a 39% increased risk (adjusted hazard ratio, 1.38; 95% CI, 1.11-1.72). In addition to expected risk factors such as older age, male sex, hypertension, and diabetes mellitus, disease activity was an important predictor of acute arterial events. Patients with the highest quartile of CRP were 54% more likely to have an acute arterial event than patients in the lowest quartile of CRP values.[9] Also, disease severity was significantly associated with events (hazard ratio, 5.40; 95% CI, 4.03-7.22).

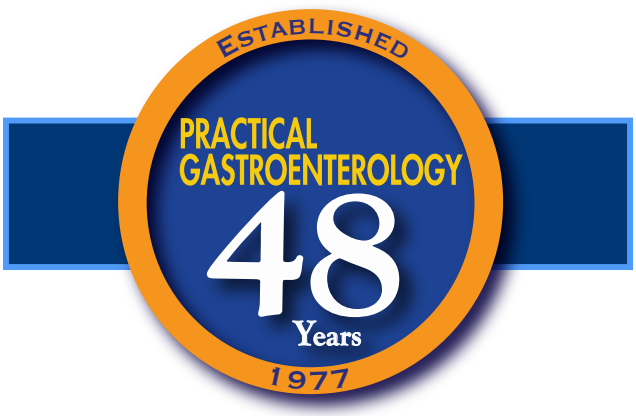
A study from the U.S. National Inpatient Sample included 2.6 million patients with myocardial infarction, including over 3600 with ulcerative colitis and over 3700 with Crohn's disease.[10] In-hospital mortality was similar for patients with both IBD subtypes along with myocardial infarction and patients without IBD who had myocardial infarction. However, length of hospital stay was significantly longer among patients with concomitant IBD, and myocardial infarction compared to those with myocardial infarction alone. Additionally, hospital costs were significantly higher in the IBD patients.[10]

The incidence of acute arterial events in IBD patients was assessed in the French National database.[11] This included over 177,000 IBD patients with over 773,000 person-years of follow-up and included over 4000 acute arterial events. The incidence of acute arterial events with stratified into 3 categories by medication use (no thiopurine or anti-TNF, thiopurine, or anti-TNF). The total incidence of all acute arterial events was 5.4 cases per 1000 person-years, and when stratified by medication category, was 5.9 per 1000 in the no thiopurine/no anti-TNF group, 3.5 per 1000 in the thiopurine group, and 2.9 per 1000 in the anti-TNF group.[11] The hazard ratio for all acute arterial events was 0.79 in the anti-TNF group. Thus, it appeared the use of anti-TNF may be protective against the development of MACE.

Even microscopic colitis may be associated with increased risk of MACE. A population-based study from Sweden was recently published and included over 11,000 patients with microscopic colitis.[12] The unadjusted hazard ratio for MACE among the microscopic colitis patients was 1.51 (95% CI, 1.44-1.59). After adjusting for 10 risk factors, the hazard ratio was 1.27 (95% CI, 1.21-1.33), and after adjusting for these 10 risk factors plus the number of healthcare visits, the hazard ratio remained significantly elevated at 1.23 (95% CI, 1.17-1.29).[12]

THROMBOEMBOLISM RISK

It has been recognized for decades that the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) is elevated among patients with IBD. A landmark population-based study from Manitoba showed that the incidence of DVT was 31 cases per 10,000 person-years in Crohn's disease and 30 per 10,000 in ulcerative colitis.[13] When compared to 10 matched controls per case, the hazard ratio for DVT in Crohn's disease was 4.7 and in ulcerative colitis was 2.8. For PE, the incidence



rate was 10.3 cases per 10,000 person-years in Crohn's disease and 19.8 per 10,000 in ulcerative colitis. When compared to matched controls, the hazard ratio for PE was 2.9 in Crohn's disease and 3.6 in ulcerative colitis.[13] The authors concluded that IBD patients have an at least threefold risk of developing thromboembolism.

In a retrospective single-center study of 98 patients with IBD and thromboembolism, we found that extensive colitis occurred in 76% of the ulcerative colitis patients, and ileocolonic or colonic disease occurred in almost 80% of Crohn's disease patients.[14] Thus, it appears that the extent of colonic inflammation may be a risk factor. When examining for specific thrombophilias, we found that about a third of IBD patients tested for thrombophilia were positive, with the most common thrombophilias being activated protein C resistance, factor V Leiden mutation, hyperhomocystinemia, and the presence of antiphospholipid antibodies.[14] Risk factors for thromboembolism among this cohort included immobility or hospitalization in the majority, prior known thrombophilia or thromboembolism, followed by malignancy and recent surgery.

RISK WITH SPECIFIC MEDICATIONS

Janus Kinase Inhibitors

In placebo-controlled trials of tofacitinib for ulcerative colitis, higher increases in total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density protein (LDL) cholesterol, and triglycerides were seen among tofacitinib-treated patients compared to those on placebo.[15] Interestingly, decreases in serum CRP concentrations correlated significantly with increases in lipids. The incidence rate of MACE was less than 1 case per 100 person-years.

The ORAL Surveillance study was mandated by the FDA to further examine the safety of tofacitinib in patients with rheumatoid arthritis who were at least 50 years old and had at least 1 cardiovascular risk factor.[16] These patients had already failed methotrexate. They were randomized in a 1:1:1 fashion to tofacitinib 5 mg b.i.d. plus methotrexate, tofacitinib 10 mg b.i.d. plus methotrexate, or either adalimumab 40 mg subcutaneously every two weeks plus methotrexate or etanercept 50 mg subcutaneously weekly plus methotrexate. The primary end points were all safety end points, including adjudicated MACE, defined as cardiovascular death, nonfatal myocardial infarction or nonfatal stroke, and adjudicated malignancies excluding non-melanoma skin cancers (NMSC). The study continued until at least 1500 subjects had been followed for three years and at least 103 adjudicated MACE had occurred and at least 138 adjudicated malignancies excluding NMSC.[16]

The FDA in 2019 issued a drug safety communication warning about the potential hazards of thromboembolism of tofacitinib based on an interim analysis of this study. The incidence of DVT/PE was 0.49 cases per 100 person-years in the tofacitinib 10 mg b.i.d. group, versus 0.07 cases per 100 person-years in the anti-TNF treated group, with an incidence rate ratio of 7. The mortality rate in the high dose tofacitinib group was 1.16 cases per 100 person-years, versus 0.63/100 person-years in the anti-TNF treated group, yielding an incidence rate ratio of 1.8. A boxed warning about thromboembolism was added to the tofacitinib label, and for all approved indications, the use of tofacitinib were restricted to those who had failed anti-TNF therapy (FDA communication, July 26, 2019).

With the final results of the ORAL Surveillance study, over 4000 patients were enrolled, and the median follow-up was four years.[16] A total of 3.4% of the tofacitinib-treated patients developed adjudicated MACE, versus 2.5% of the anti-TNF-treated patients. The incidence rate of MACE was 0.98 cases per 100 person-years with tofacitinib and 0.73 cases per 100 person-years with TNF inhibitors. The hazard ratio for MACE with tofacitinib relative to TNF inhibitors was 1.3 (95% CI, 0.9-1.9). Since the pre-specified endpoint for non-inferiority was that the upper limit of the 95% CI would be less than 1.8, non-inferiority for

tofacitinib was not met.[16] For adjudicated cancers, a total of 4.2% of the tofacitinib-treated patients developed malignancy, versus 2.9% of the TNF inhibitor-treated patients. The incidence rate of cancer was 1.13 cases per 100 person-years with tofacitinib and 0.77 per 100 with TNF inhibitors. The hazard ratio for malignancy excluding NMSC with tofacitinib was 1.48 (95% CI, 1.04-2.09), and therefore the primary endpoint of non-inferiority versus TNF inhibitors was not met for this endpoint, too.[16]

Several groups have examined in more detail the risk factors for MACE and malignancies within this study cohort. In one analysis, patients who were older than 65 years and were either current or former cigarette smokers were considered the high-risk group (n=2821), whereas patients who were younger than 65 years and had never smoked were considered low-risk patients (n=1541).[17] In the low-risk category, there was no longer a significant increase in incidence rate of malignancies excluding NMSC, MACE, myocardial infarction, venous thromboembolism (VTE), or all-cause mortality. Furthermore, when the cumulative incidence of end points was stratified by the high-risk and low-risk categories, it was clear that the differences in cumulative risk between tofacitinib and anti-TNFs seen in the high-risk population were no longer seen in the low-risk population.[17] This would suggest that there is a population of patients (younger than 65 years and nonsmokers) who would benefit from tofacitinib and not be at increased risk for these safety events.

In the OCTAVE Open clinical trial program for ulcerative colitis, a total of four PE events were seen, all of whom had at least one risk factor for PE, and 1 DVT event was seen in a patient who had at least 3 risk factors for DVT.[18] In an integrated safety analysis of the entire global clinical program of tofacitinib in ulcerative colitis, which included phase 2 and phase 3 trials, and an interim analysis of a phase 3b/4 study, the mortality rate was 0.2 deaths per 100 person-years, and the incidence rates for MACE was 0.3 cases per 100, for malignancies excluding non-melanoma skin cancers was 0.8/100, for DVT was 0 cases per 100, and for PE was 0.2 cases per 100.[19]

In the upadacitinib clinical programs for ulcerative colitis and Crohn's disease, there does not appear to be a strong signal for either VTE or MACE. In the phase 3 U-ACHIEVE maintenance study, there were no VTE events seen in patients treated with placebo or upadacitinib 15 mg daily.[20] There were two patients on the 30 mg dose of upadacitinib who had VTE, for an incidence rate of 1.5 cases per 100 person-years. There were no MACE events seen in patients treated with either dose of upadacitinib in this same study.[20] In the U-ENDURE maintenance study of upadacitinib in Crohn's disease, there were no venous thromboembolic events seen in patients treated with placebo or upadacitinib 15 mg daily.[21] There was a single case of hepatic vein thrombosis concurrent with an exacerbation of Crohn's disease in a patient treated with 30 mg daily of upadacitinib, for an incidence rate of 0.6 cases per 100 person-years. There were no MACE events seen in U-ENDURE.[21] An integrated analysis of MACE and VTE across the rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis phase 2b/3 clinical programs of upadacitinib was performed.[22] The incidence rates of MACE ranged from 0.3 to 0.6 events per 100 person-years in the rheumatoid arthritis and psoriatic arthritis trials. There were no MACE events seen in the ankylosing spondylitis trials. Similarly, for VTE, incidence rates ranged from 0.2 to 0.4 cases per 100 person-years in these trials.[22]

The comparative cardiovascular safety of tofacitinib and anti-TNF agents were compared in a United States insurance claims database, which included 305 IBD patients on tofacitinib and over 19,000 patients on anti-TNF therapy.[23] A total of 5% of tofacitinib-treated patients and 3% of anti-TNF-treated patients developed VTE. Four percent of tofacitinib-treated patients and 3% of anti-TNF-treated patients developed cardiovascular events. MACE occurred in 2% of tofacitinib-treated patients and 1% of anti-TNF-treated patients.[23] The hazard ratio for VTE with tofacitinib relative to anti-TNF therapy was 1.7 (95% CI, 0.7-3.0), and for cardiovascular events was 2.5 (95% CI, 0.4-6.2).

Anti-Interleukin Antibodies

In the psoriasis and psoriatic arthritis literature, there have been conflicting data as to whether or not cardiovascular events are associated with

the use of ustekinumab. A different monoclonal antibody to interleukins-12 and -23, briakinumab, had demonstrated an increased risk of MACE.[24] For example, in a study of two U.S. commercial insurance claims databases, the incidence rates of atrial fibrillation and MACE were determined among over 60,000 patients with psoriasis or psoriatic arthritis treated with either ustekinumab or anti-TNF therapy.[25] Incidence rates of atrial fibrillation were 5.0 cases per 1000 person-years for ustekinumab-treated patients and 4.7 per 1000 for anti-TNF-treated patients. For MACE, the incidence rates were 6.2 cases per 1000 person-years for ustekinumab and 6.1/1000 for anti-TNF therapy.[25] The adjusted HR for atrial fibrillation among those treated with ustekinumab was 1.1 (95% CI, 0.8-1.52). The authors concluded that there was significantly different risk of atrial fibrillation of MACE.

In a pooled safety analysis of phase 2 and phase 3 studies of ustekinumab for Crohn's disease and ulcerative colitis, there were 2 adjudicated MACE events in the ulcerative colitis patients: one patient with nonfatal myocardial infarction and one nonfatal stroke.[26] Additionally, there was one patient with acute myocardial infarction perioperatively, who ultimately succumbed to acute respiratory distress syndrome (ARDS) and was categorized as a cardiovascular death. In Crohn's disease, there was one adjudicated non-fatal stroke. DVT/PE events were reported in 13 ustekinumab patients for a total of 0.75 patients per 100 person-years.

In the FORTIFY phase 3 maintenance study of risankizumab for Crohn's disease, there were no MACE events reported in either of the risankizumab-treated patient groups.[27]

Sphingosine-1-Phosphate Receptor Modulators

Activating cardiac sphingosine-1-phosphate (S1P) receptors may affect heart rate and cardiac contractility, protect from ischemia, induced hypertrophy, and mobilize intracellular calcium. Conversely, blocking S1P receptor activation may disrupt potassium channels in cardiac myelocytes and interrupt cardiac conduction by hyper polarizing myelocytes.

There are two S1P receptor modulators that are now approved for moderately to severely active ulcerative colitis, ozanimod and etrasimod. Ozanimod selectively blocks the S1 P1 and S1 P5 receptors, whereas etrasimod blocks S1 P4 in addition to S1 P1 and S1 P5. There may be more cytochrome P450 interactions with ozanimod versus etrasimod. The half-life of ozanimod is 21 hours, but there is an active metabolite with a half-life of 11 days. The half-life of etrasimod is approximately 33 hours. There appears to be first dose heart rate reduction with both medications. Ozanimod has a dose titration regimen for the first week, whereas there is no dosed titration with etrasimod. It is recommended that patients get an ophthalmic exam if they have risk factors for macular edema with ozanimod, and it is recommended that all patients starting etrasimod get a baseline ophthalmic exam. Fortunately, there were only a few MACE events or VTE events associated with ozanimod in the phase 2 and phase 3 ulcerative colitis studies, for a cumulative exposure of over 2200 person-years.[28] There were no myocardial infarctions, three patients with ischemic strokes, four patients with VTE, and one patient with sudden death. Ozanimod has been shown to be a weak monoamine oxidase inhibitor, and thus theoretically could cause serotonin syndrome in patients who are also on selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors. In one analysis of adverse events which could theoretically be part of serotonin syndrome, including pyrexia, nausea, hypothermia, tremor, and tachycardia, the incidence of these events was not significantly higher among patients on SSRIs or SNRIs compared to those not on these medications.[29] In the multiple sclerosis literature, an open-label study of ozanimod demonstrated no increase in adverse events which theoretically were symptoms of serotonin syndrome in patients on SSRI/SNRI.[30]

Recently, there have been several systematic reviews and meta-analyses of the risk of MACE among IBD patients, stratified by medications. In one systematic review, there were 22 randomized controlled trials involving over 12,000 patients with Crohn's disease, and 32 randomized trials involving over 22,000 patients with ulcerative colitis. The authors concluded that there was no impact on the risk of MACE among Crohn's disease patients with any of the biologics (i.e., anti-TNF

agents, anti-integrins, anti-interleukins). Among 32 randomized trials involving over 22,000 ulcerative colitis patients, there was similarly no impact on the risk of MACE among the ulcerative colitis patients (anti-TNF, anti-integrin, anti-interleukin, JAK inhibitor).[31] Another systematic review and meta-analysis examined the risk of MACE among patients treated with biologics or small molecules for multiple immune-mediated inflammatory disorders, including IBD, psoriasis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis.[32] There were 36 randomized control trials and 4 cohort studies including over 126,000 patients. This analysis detected an increased risk of MACE with anti-IL-12/23 medications relative to placebo, with OR of 3.15 (credible interval [CrI], 1.01-13.35), with anti-TNF agents (OR, 2.49; CrI, 1.14-5.62), and with JAK inhibitors (OR, 2.64; CrI, 1.26-5.99). No increased risk of MACE was seen with the anti-p19 anti-IL-23 agents (OR, 2.65; CrI, 0.85-10.03). No difference in the risk of MACE was seen between drug classes or between disease states.

CONCLUSIONS

MACE will continue to be an important outcome in IBD trials. The definition of MACE can vary across studies so definitions need to be checked before making cross-comparisons. Despite fewer conventional coronary artery disease risk factors, there does appear to be an increased risk of cardiovascular and cerebrovascular events in IBD patients. Therefore, patients with chest pain probably need a thorough evaluation, even if they are younger, female, etc. In addition, thromboembolism occurs with more frequency in IBD patients, likely due to increased inflammation and more colonic involvement. There is no one specific thrombophilia that is increased. Hospitalized patients should be on VTE prophylaxis. Finally, there is no clear-cut signal of increased MACE with specific medications. The results of the ORAL Surveillance study in rheumatoid arthritis may not necessarily be translatable to the IBD population and may not be able to be extrapolated to JAK inhibitors as a whole. Certainly, there does not appear to be an increased risk of MACE among patients under the age of 65 years who are never smokers. ■

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Answers to this month's crossword puzzle:

1 M	O	2 D	U	3 L	A	4 T	E	■	5 F	6 I	B	7 E	R	8 S
E	■	R	■	U	■	A	■	9 I	■	N	■	R	■	E
10 T	R	I	A	L	■	11 C	E	L	L	U	L	O	S	E
A	■	F	■	L	■	T	■	E	■	L	■	D	■	■
12 B	I	T	E	■	13 V	I	R	U	14 C	I	D	E	■	15 P
O	■	■	■	16 M	■	L	■	17 S	U	N	■	■	18 S	E
19 L	E	U	20 C	I	21 N	E	■	■	T	■	22 G	23 U	A	R
I	■	■	24 O	C	A	■	■	■	■	25 V	■	26 P	R	■
27 T	U	28 M	O	R	■	29 D	Y	30 S	B	I	O	S	I	31 S
E	■	A	■	O	■	Y	■	E	■	S	■	■	■	C
32 S	O	L	U	B	L	E	■	33 C	R	C	■	34 F	D	A
■	■	A	■	I	■	■	■	R	■	E	■	A	■	R
35 A	D	I	P	O	S	36 E	■	37 E	R	R	A	T	I	C
C	■	S	■	T	■	G	■	T	■	A	■	T	■	E
38 T	R	E	M	A	T	O	D	E	■	39 L	A	Y	E	R